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FIG. 1A

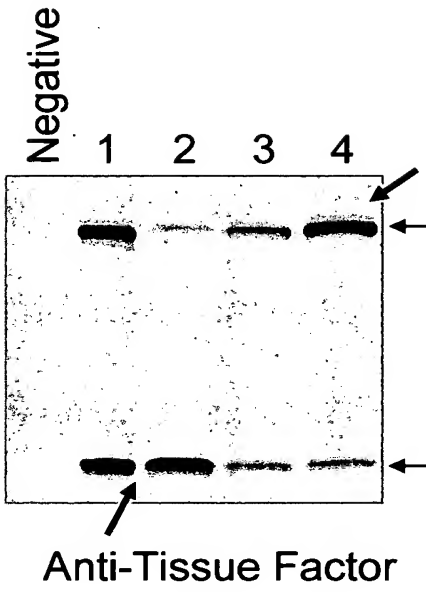


FIG. 1B

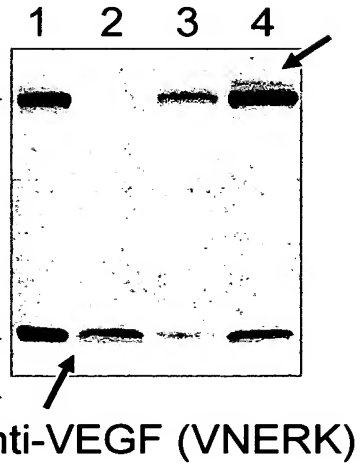


FIG. 2

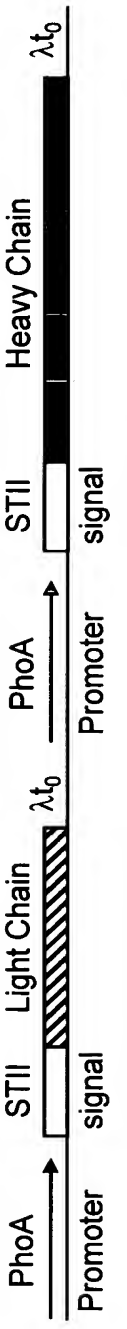

PhoA
Promoter
STII
signal
Light Chain
λt0
PhoA
Promoter
STII
signal
Heavy Chain
λt0

FIG. 3A

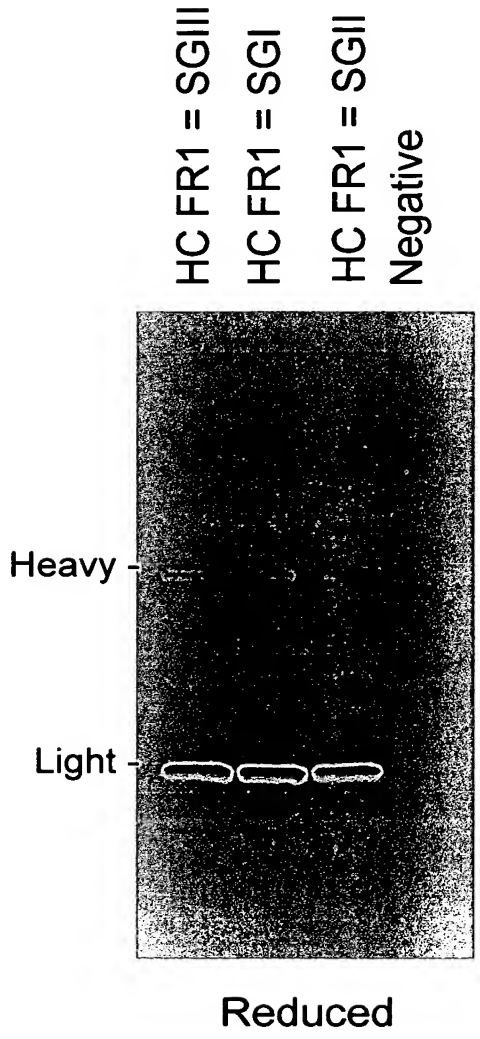

HC FR1 = SGIII
HC FR1 = SGI
HC FR1 = SGII
Negative
Heavy
Light
Reduced

FIG. 3B

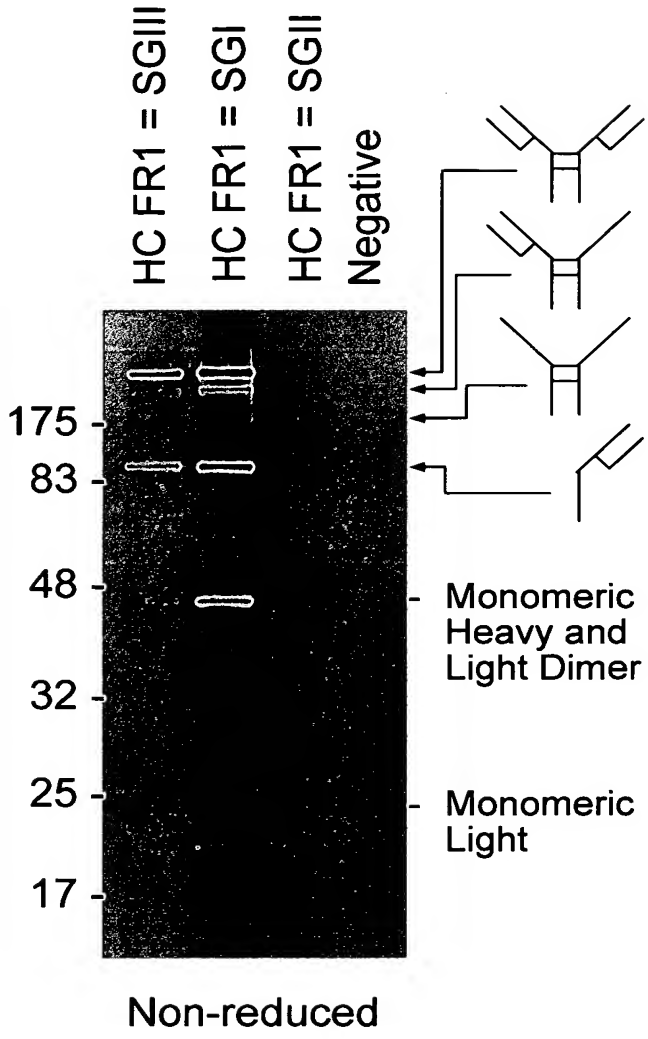

HC FR1 = SGIII
HC FR1 = SGI
HC FR1 = SGII
Negative
175
83
48
32
25
17
Monomeric Heavy and Light Dimer
Monomeric Light
Non-reduced

FIG. 4A

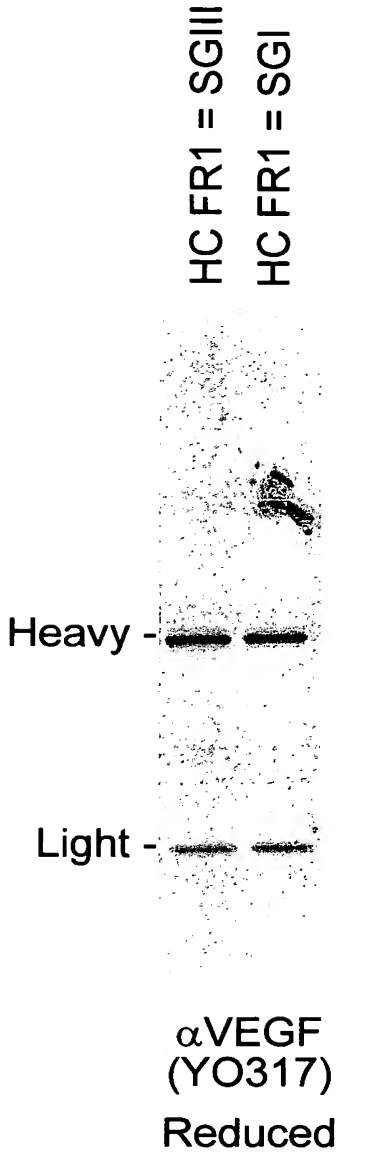

HC FR1 = SGIII
HC FR1 = SGI
Heavy
Light
αVEGF
(YO317)
Reduced

FIG. 4B

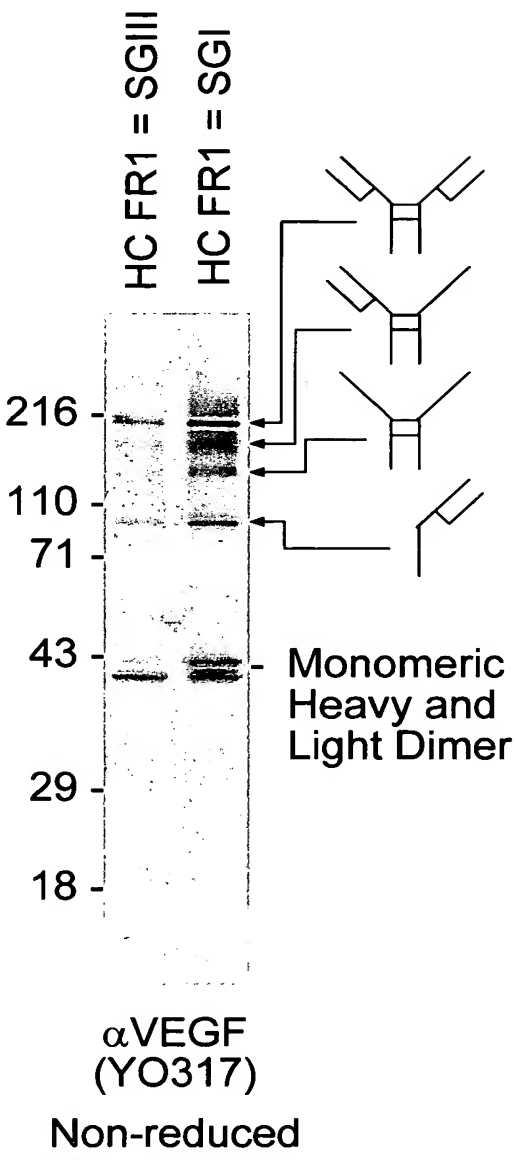

HC FR1 = SGIII
HC FR1 = SGI
216
110
71
43
29
18
Monomeric
Heavy and
Light Dimer
αVEGF
(YO317)
Non-reduced

FIG. 5A

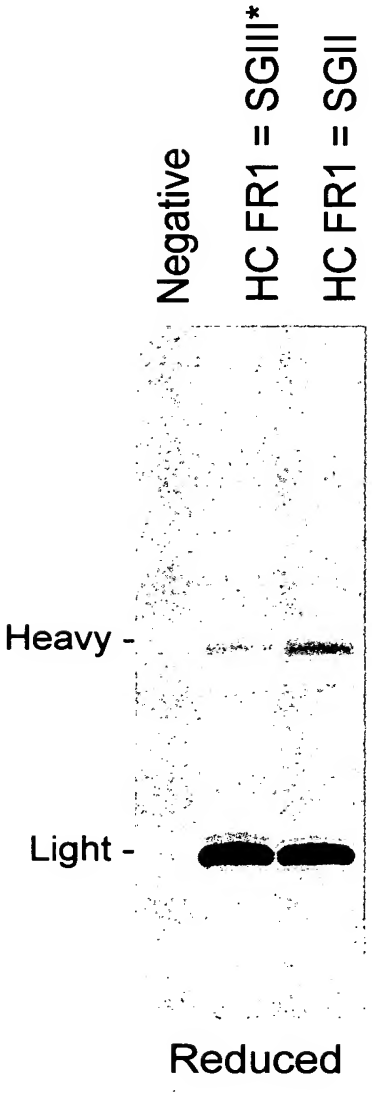
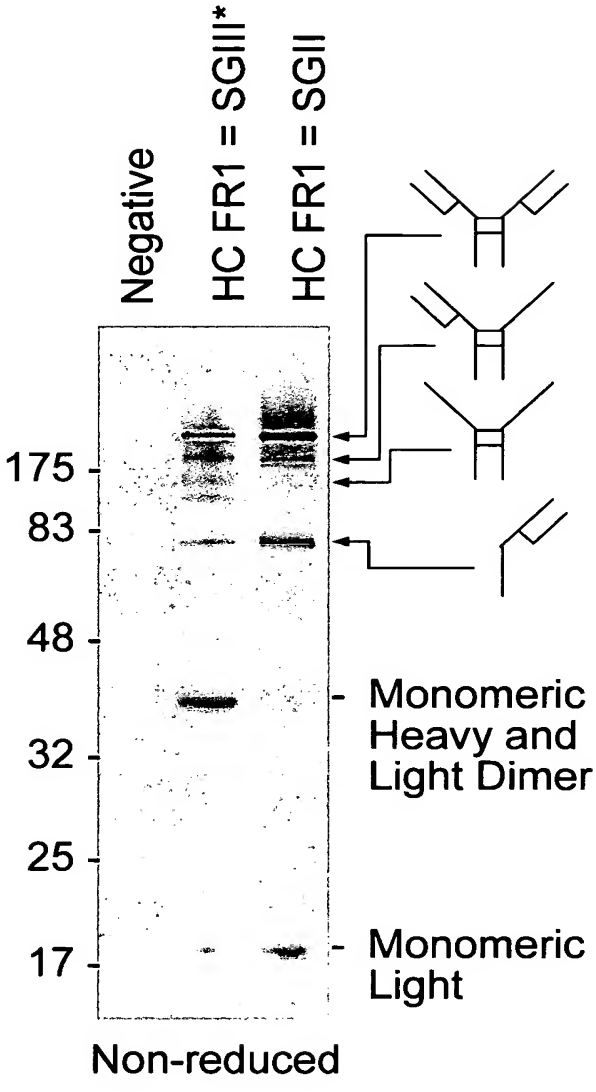


FIG. 5B



*Includes an A24V change as part of humanization.

FIG. 6A

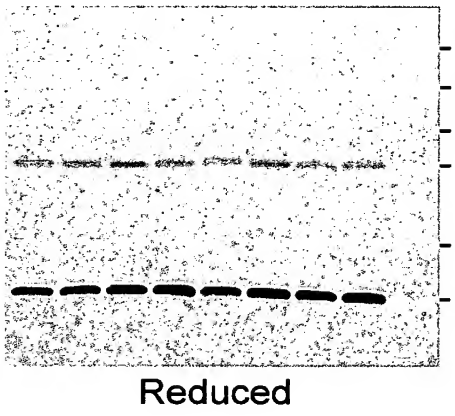


FIG. 6B

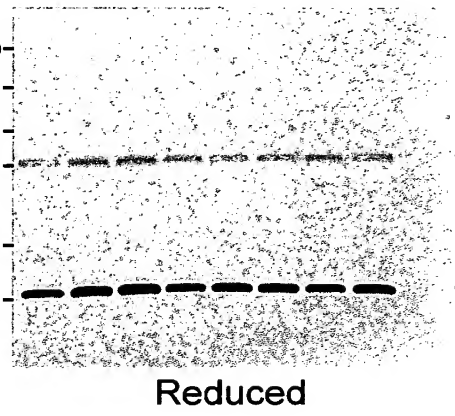


FIG. 6C

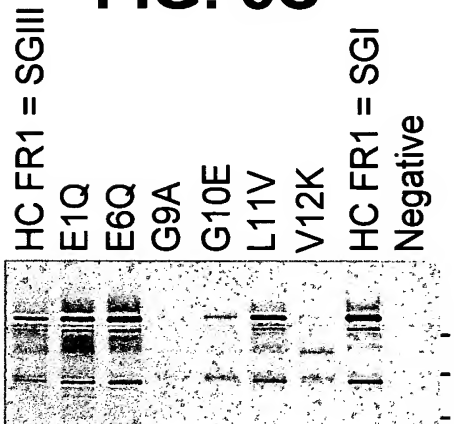


FIG. 6D

FIG. 7A

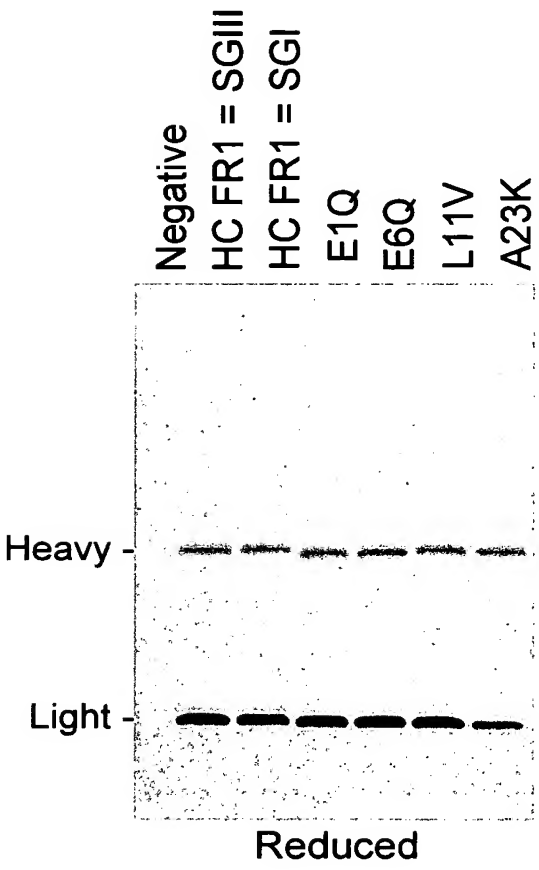

Negative
HC FR1 = SGIII
HC FR1 = SGI
E1Q
E6Q
L11V
A23K
Heavy
Light
Reduced

FIG. 7B

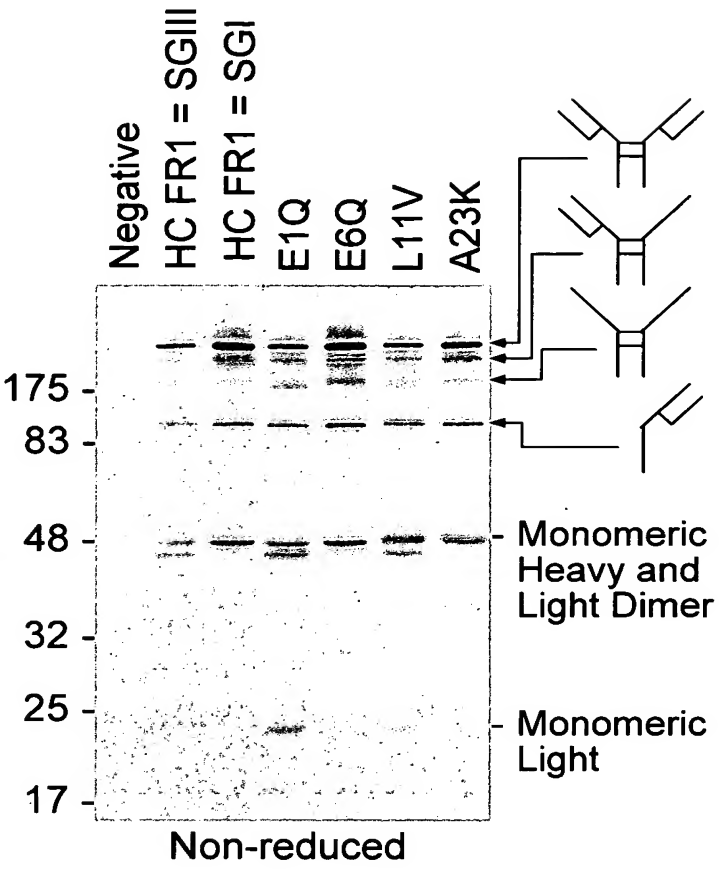

Negative
HC FR1 = SGIII
HC FR1 = SGI
E1Q
E6Q
L11V
A23K
175
83
48
32
25
17
Monomeric Heavy and Light Dimer
Monomeric Light
Non-reduced

FIG. 8A

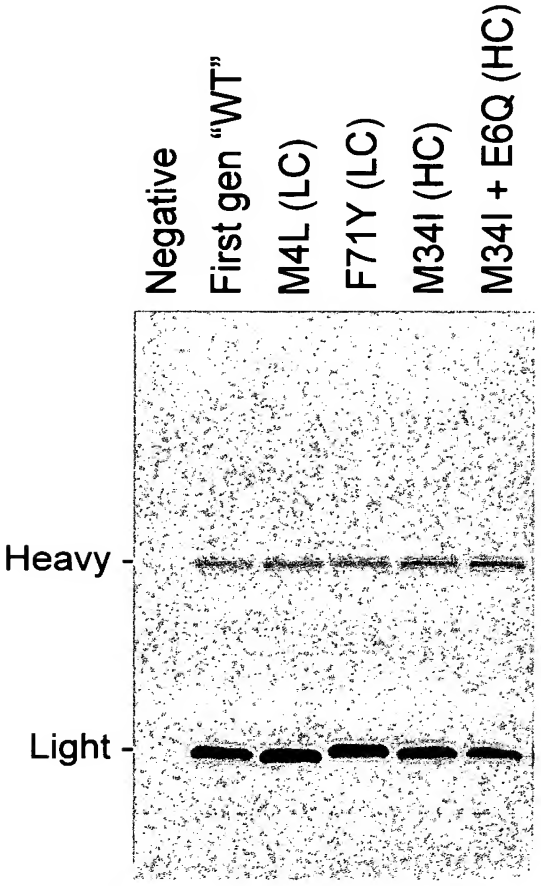

Negative
First gen "WT"
M4L (LC)
F71Y (LC)
M34I (HC)
M34I + E6Q (HC)
Heavy
Light

FIG. 8B

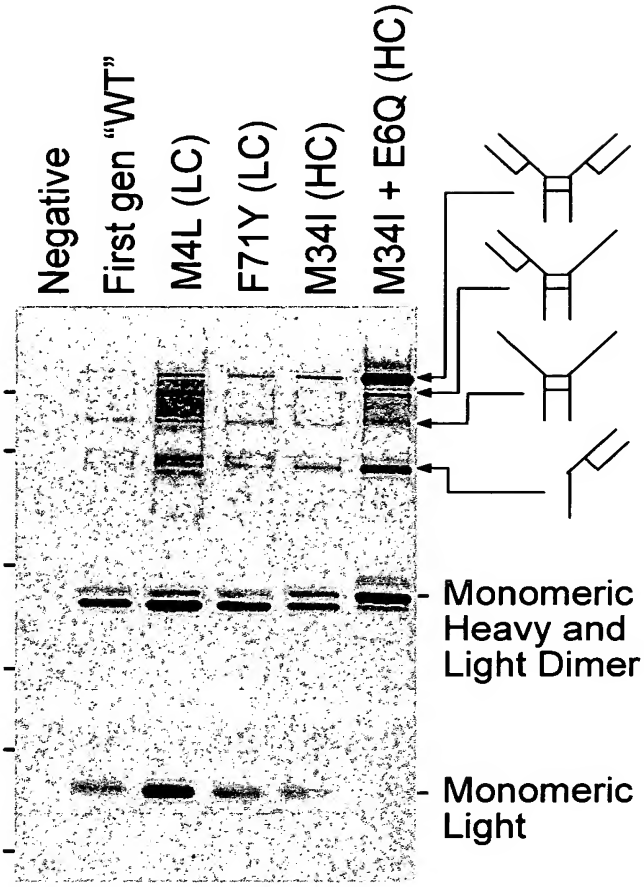

Negative
First gen "WT"
M4L (LC)
F71Y (LC)
M34I (HC)
M34I + E6Q (HC)
175
83
48
32
25
17
Monomeric Heavy and Light Dimer
Monomeric Light

FIG. 9A

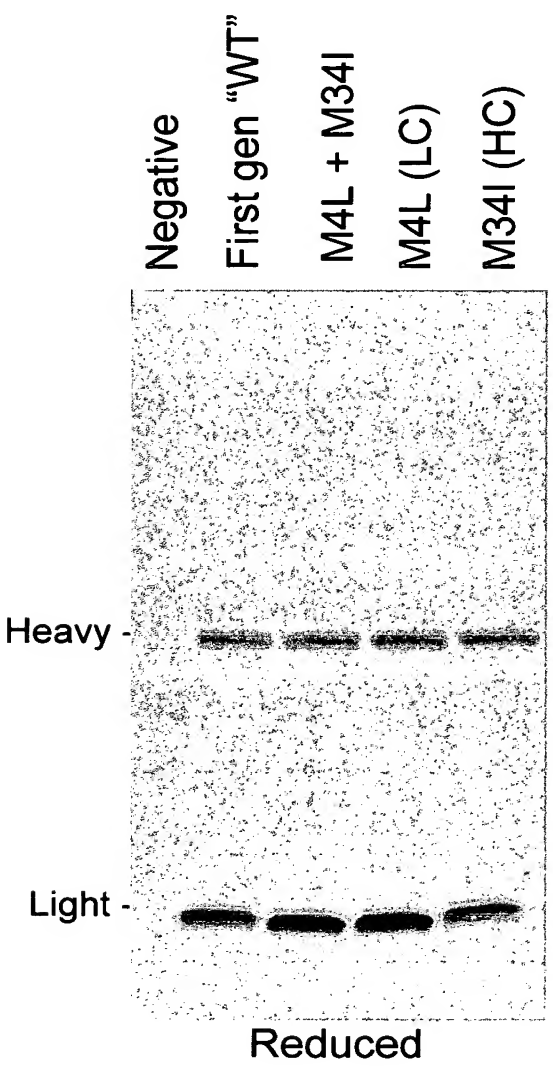

Negative
First gen "WT"
M4L + M34I
M4L (LC)
M34I (HC)
Heavy
Light
Reduced

FIG. 9B

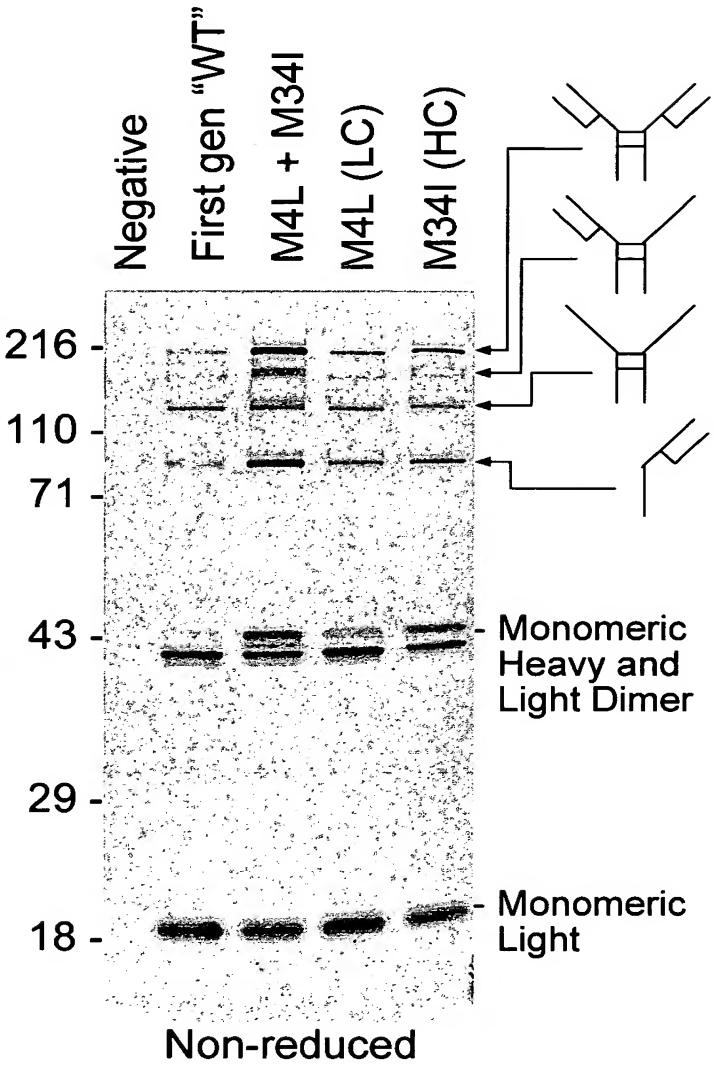

Negative
First gen "WT"
M4L + M34I
M4L (LC)
M34I (HC)
216
110
71
43
29
18
Monomeric Heavy and Light Dimer
Monomeric Light
Non-reduced

FIG. 10A

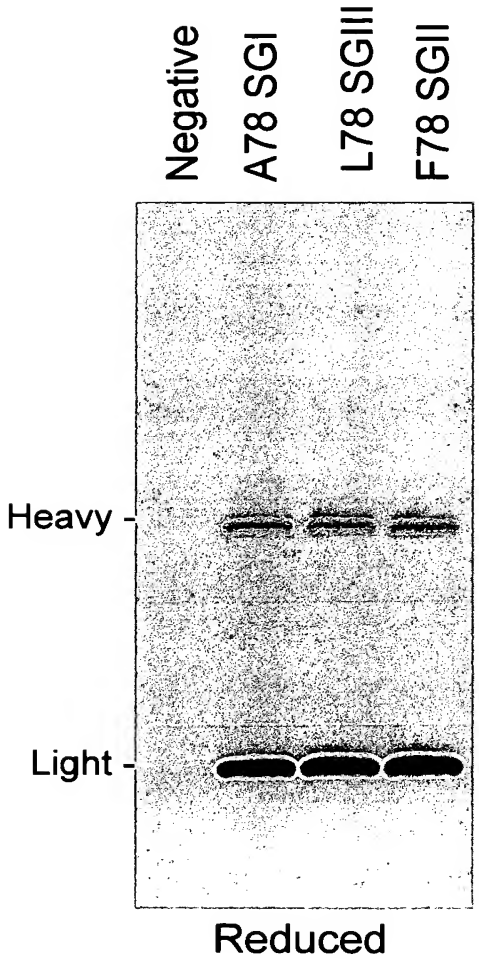


FIG. 10B

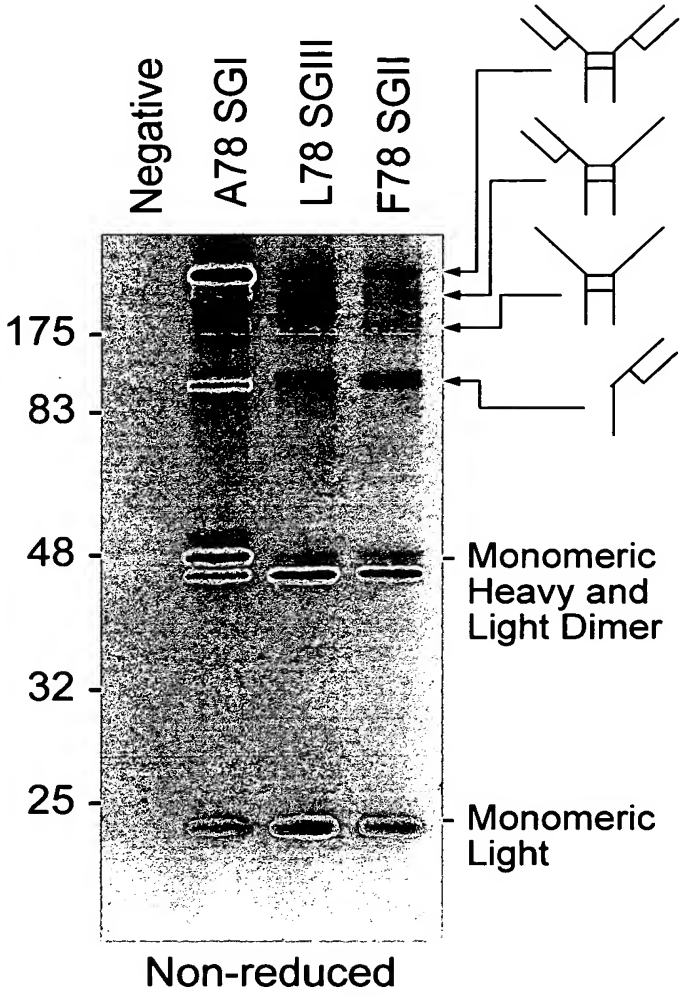


FIG. 11A

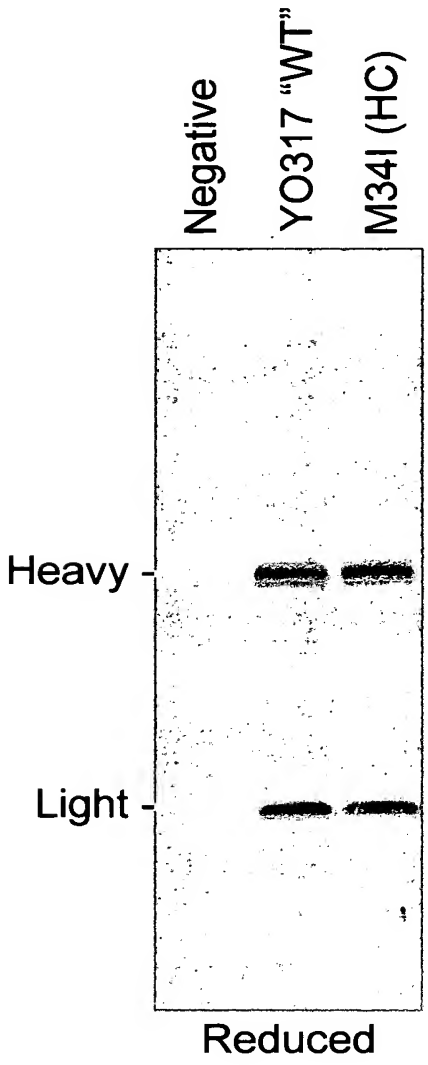


FIG. 11B

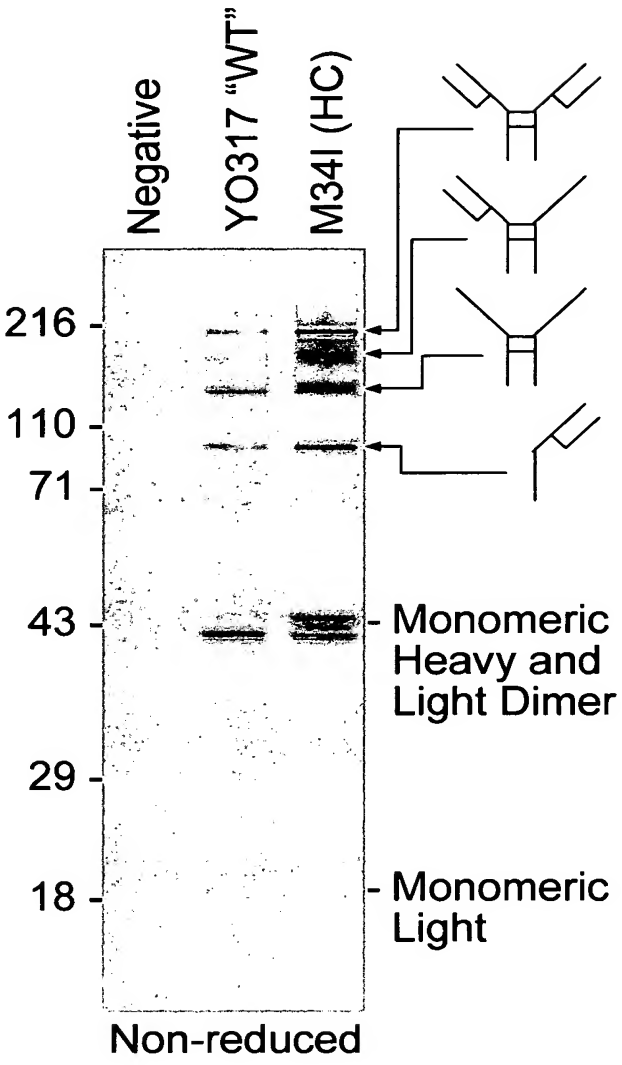


FIG. 12A

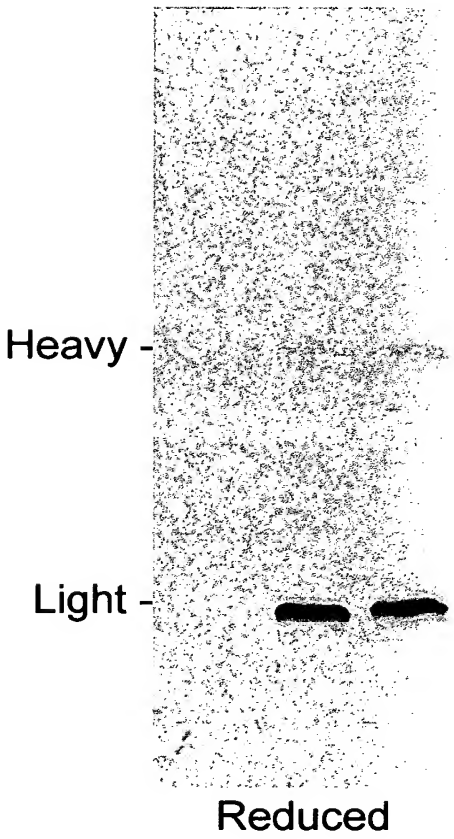


FIG. 12B

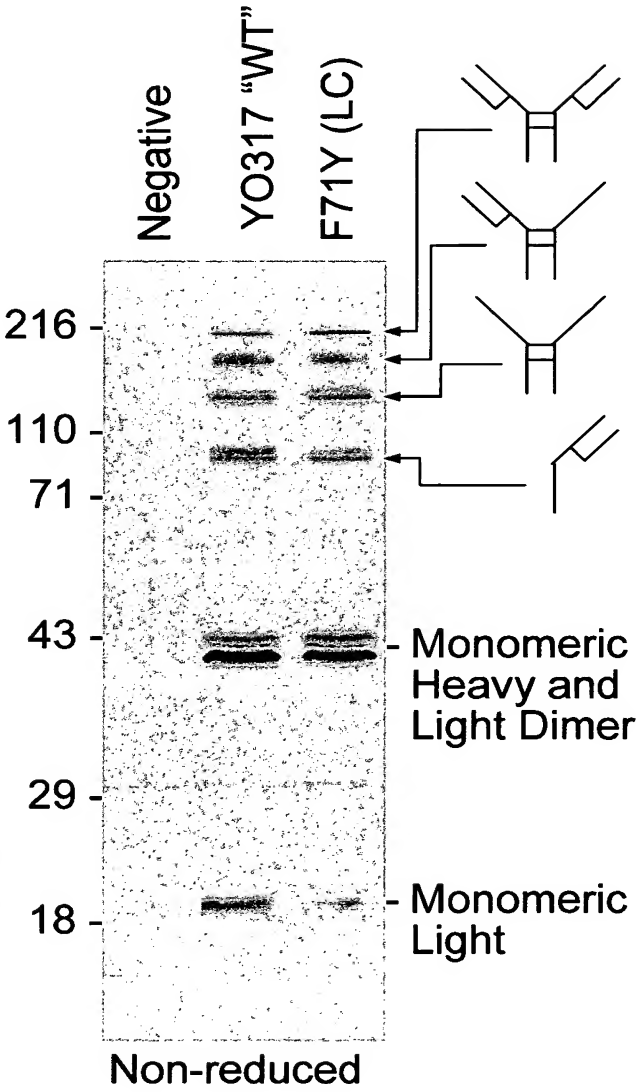
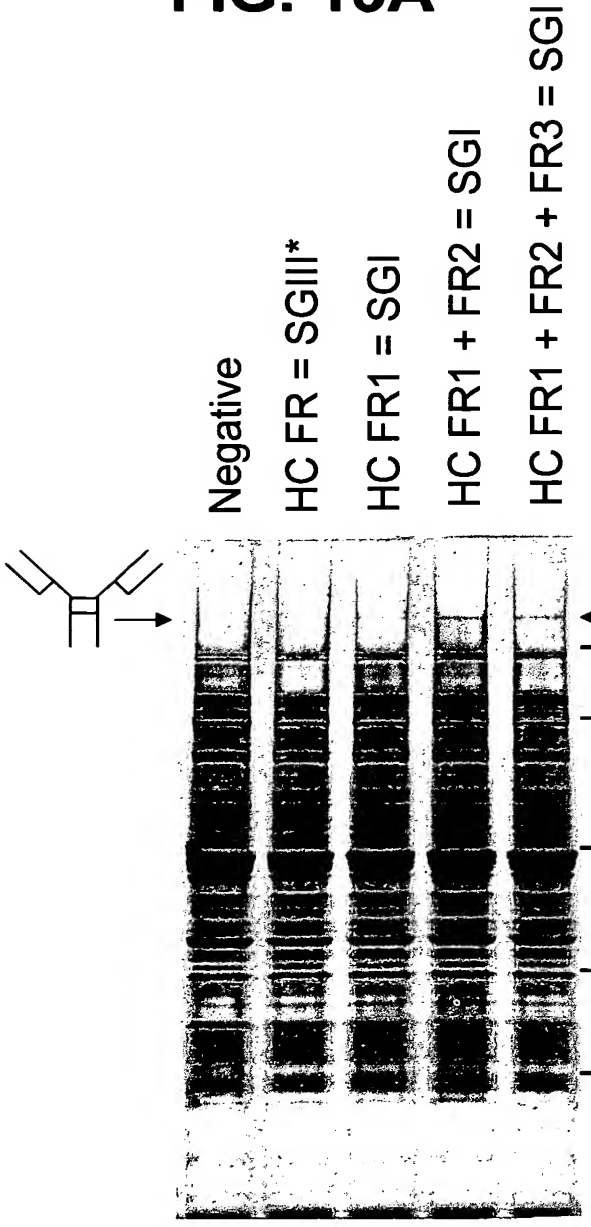
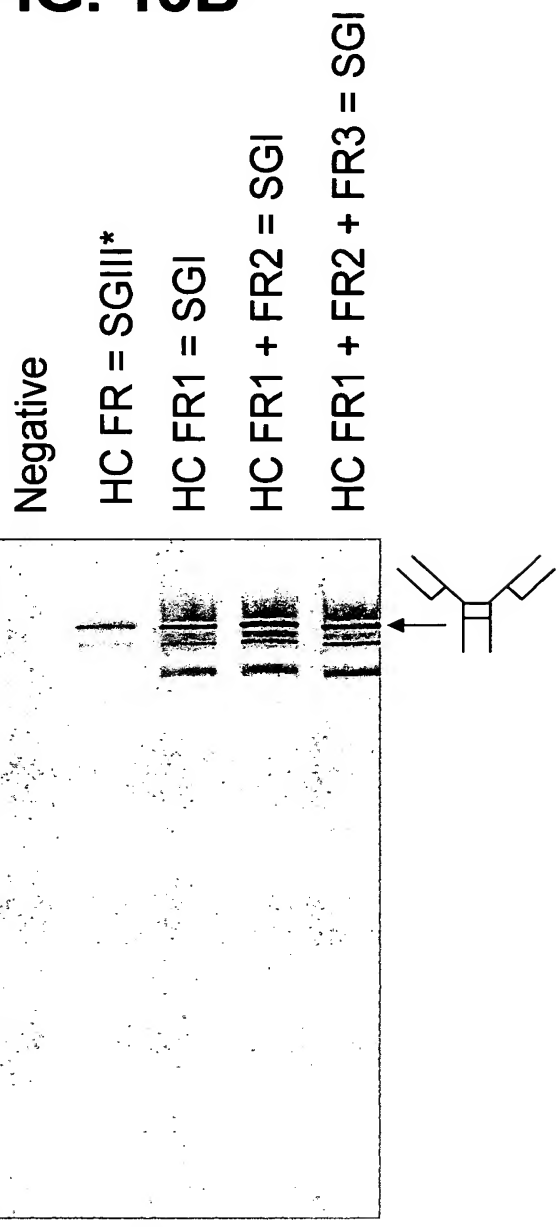


FIG. 13A



Coomassie Stain
Soluble Fraction

FIG. 13B



αFc Blot
Soluble Fraction

* Except for residues changed during humanization.

FIG. 14A FIG. 14B

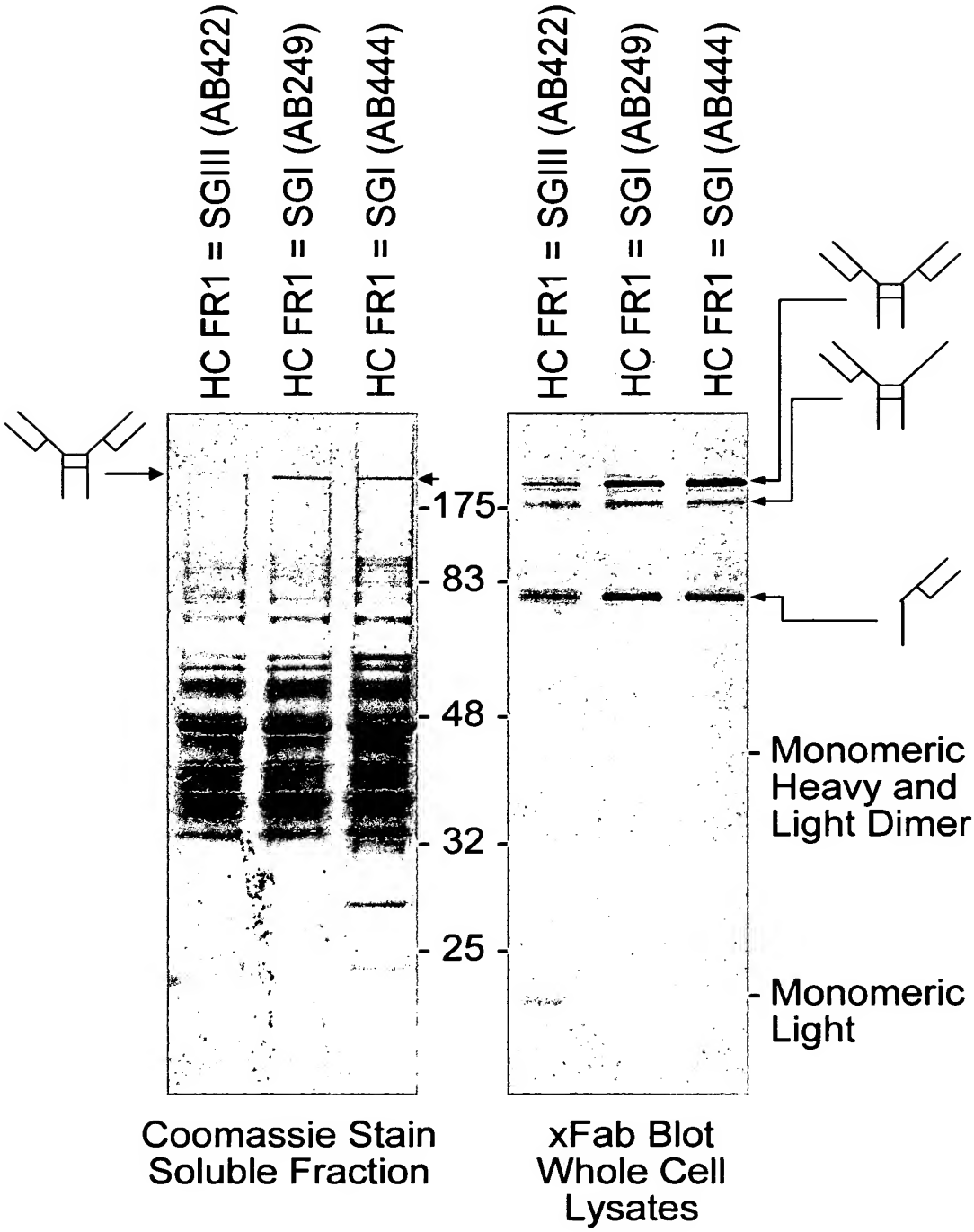


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FIG. 15A

```
  1 GAATTCAACT TCTCCATACT TTGGATAAGG AAATACAGAC ATGAAAAATC TCATTGCTGA GTTGTTATTT AAGCTTGCCC AAAAAGAAGA AGAGTCGAAT
    CTTAAGTTGA AGAGGTATGA AACCTATTCC TTTATGTCTG TACTTTTTAG AGTAACGACT CAACAATAAA TTCGAACGGG TTTTTCTTCT TCTCAGCTTA

101 GAACTGTGTG CGCAGGTAGA AGCTTTGGAG ATTATCGTCA CTGCAATGCT TCGCAATATG GCGCAAAATG ACCAACAGCG GTTGATTGAT CAGGTAGAGG
    CTTGACACAC GCGTCCATCT TCGAAACCTC TAATAGCAGT GACGTTACGA AGCGTTATAC CGCGTTTTAC TGGTTGTCGC CAACTAACTA GTCCATCTCC

201 GGGCGCTGTA CGAGGTAAAG CCCGATGCCA GCATTCCTGA CGACGATACG GAGCTGCTGC GCGATTACGT AAAGAAGTTA TTGAAGCATC CTCGTCAGTA
    CCCGCGACAT GCTCCATTTC GGGCTACGGT CGTAAGGACT GCTGCTATGC CTCGACGACG CGCTAATGCA TTTCTTCAAT AACTTCGTAG GAGCAGTCAT

301 AAAAGTTAAT CTTTTCAACA GCTGTCATAA AGTTGTCACG GCCGAGACTT ATAGTCGCTT TGTTTTTATT TTTTAATGTA TTTGTAACTA GTACGCAAGT
    TTTTCAATTA GAAAAGTTGT CGACAGTATT TCAACAGTGC CGGCTCTGAA TATCAGCGAA ACAAAAATAA AAAATTACAT AAACATTGAT CATGCGTTCA

401 TCACGTAAAA AGGGTATCTA GAATTATGAA GAAGAATATC GCATTTCTTC TTGCATCTAT GTTCGTTTTT TCTATTGCTA CAAACGCGTA CGCTGATATC
    AGTGCATTTT TCCCATAGAT CTTAATACTT CTTCTTATAG CGTAAAGAAG AACGTAGATA CAAGCAAAAA AGATAACGAT GTTTGCGCAT GCGACTATAG
  1                         M  K  K  N  I  A  F  L  L  A  S  M  F  V  F  S  I  A  T  N  A  Y  A  D  I
                            ^STII Signal TIR -1                                          anti-VEGF Light Chain^

501 CAGTTGACCC AGTCCCCGAG CTCCCTGTCC GCCTCTGTGG GCGATAGGGT CACCATCACC TGCAGCGCAA GTCAGGATAT TAGCAACTAT TTAAACTGGT
    GTCAACTGGG TCAGGGGCTC GAGGGACAGG CGGAGACACC CGCTATCCCA GTGGTAGTGG ACGTCGCGTT CAGTCCTATA ATCGTTGATA AATTTGACCA
 26 Q  L  T  Q   S  P  S   S  L  S   A  S  V  G   D  R  V   T  I  T   C  S  A  S   Q  D  I   S  N  Y   L  N  W  Y
                                                                ^variable light (VL) cys

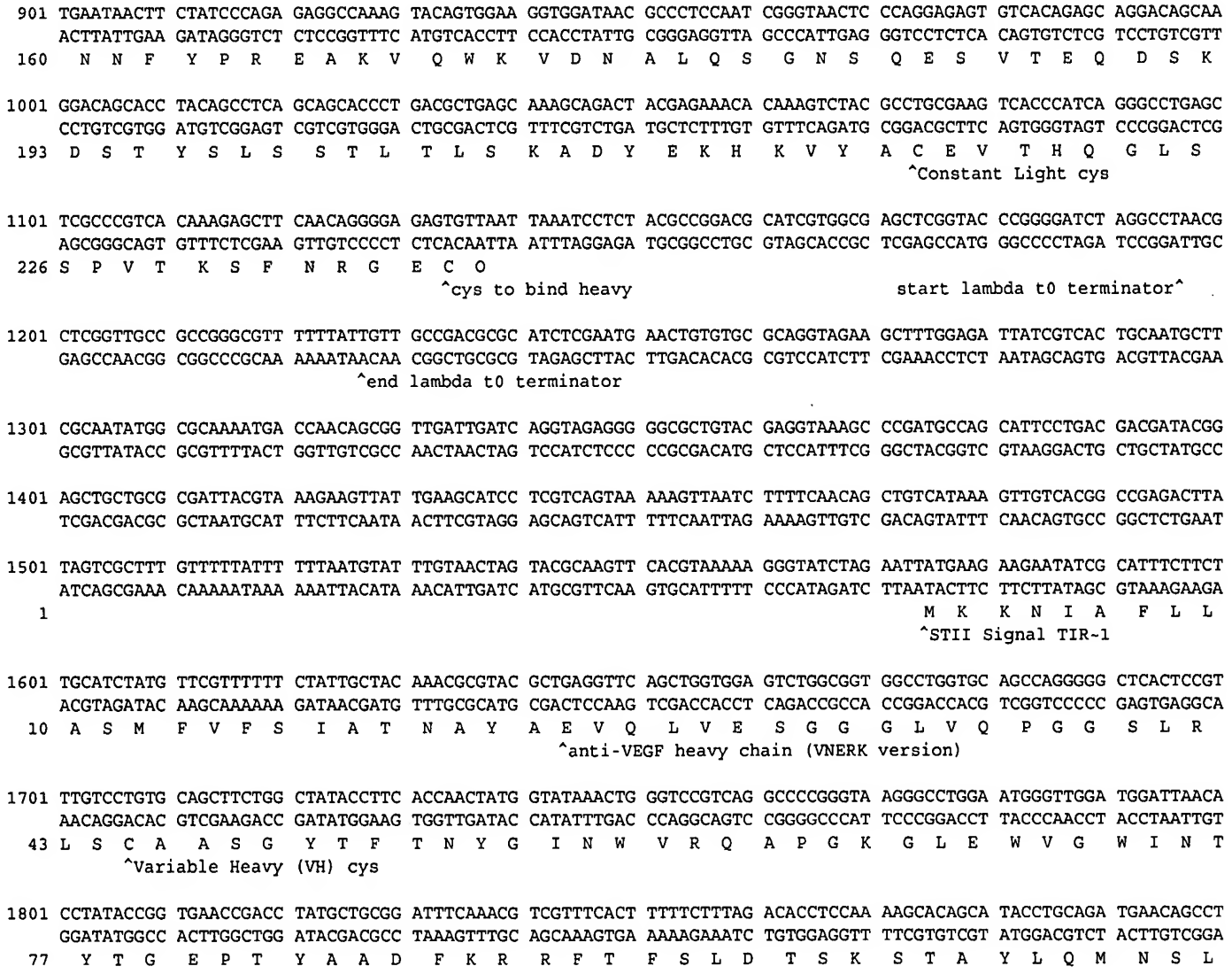
601 ATCAACAGAA ACCAGGAAAA GCTCCGAAAG TACTGATTTA CTTCACCTCC TCTCTCCACT CTGGAGTCCC TTCTCGCTTC TCTGGATCCG GTTCTGGGAC
    TAGTTGTCTT TGGTCCTTTT CGAGGCTTTC ATGACTAAAT GAAGTGGAGG AGAGAGGTGA GACCTCAGGG AAGAGCGAAG AGACCTAGGC CAAGACCCTG
 60   Q  Q  K   P  G  K   A  P  K  V   L  I  Y   F  T  S   S  L  H  S   G  V  P   S  R  F   S  G  S  G   S  G  T

701 GGATTTCACT CTGACCATCA GCAGTCTGCA GCCAGAAGAC TTCGCAACTT ATTACTGTCA ACAGTATAGC ACCGTGCCGT GGACGTTTGG ACAGGGTACC
    CCTAAAGTGA GACTGGTAGT CGTCAGACGT CGGTCTTCTG AAGCGTTGAA TAATGACAGT TGTCATATCG TGGCACGGCA CCTGCAAACC TGTCCCATGG
 93  D  F  T   L  T  I  S   S  L  Q   P  E  D   F  A  T  Y   Y  C  Q   Q  Y  S   T  V  P  W   T  F  G   Q  G  T
                                                                ^Variable light cys

801 AAGGTGGAGA TCAAACGAAC TGTGGCTGCA CCATCTGTCT TCATCTTCCC GCCATCTGAT GAGCAGTTGA AATCTGGAAC TGCTTCTGTT GTGTGCCTGC
    TTCCACCTCT AGTTTGCTTG ACACCGACGT GGTAGACAGA AGTAGAAGGG CGGTAGACTA CTCGTCAACT TTAGACCTTG ACGAAGACAA CACACGGACG
126 K  V  E  I   K  R  T   V  A  A   P  S  V  F   I  F  P   P  S  D   E  Q  L  K   S  G  T   A  S  V   V  C  L  L
                                                                                    Constant Light cys^
```

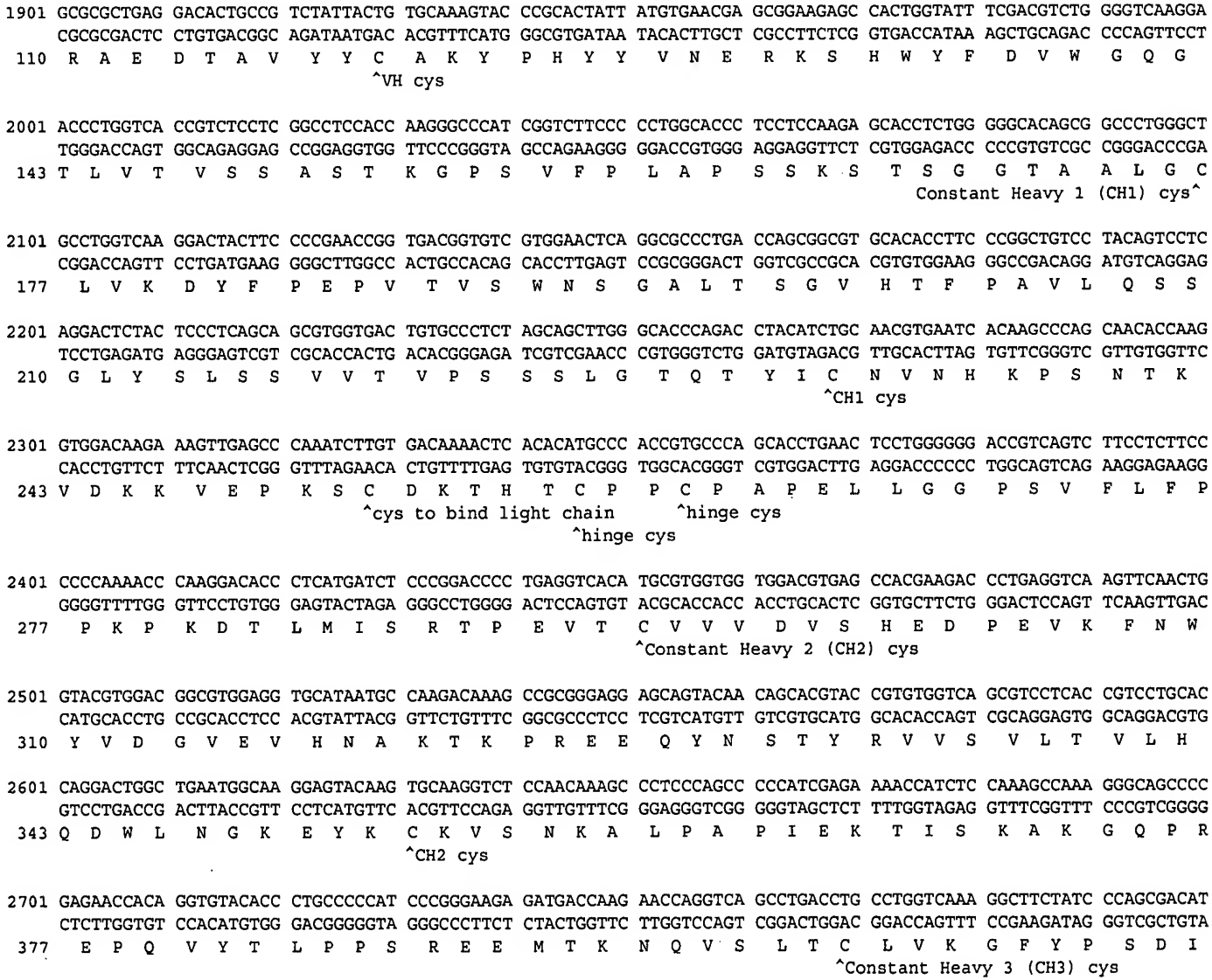
Inventor: SIMMONS
Docket No.: 11669.120US01
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
Serial No.: 10/764,428
Sheet 15 of 50

FIG. 15B



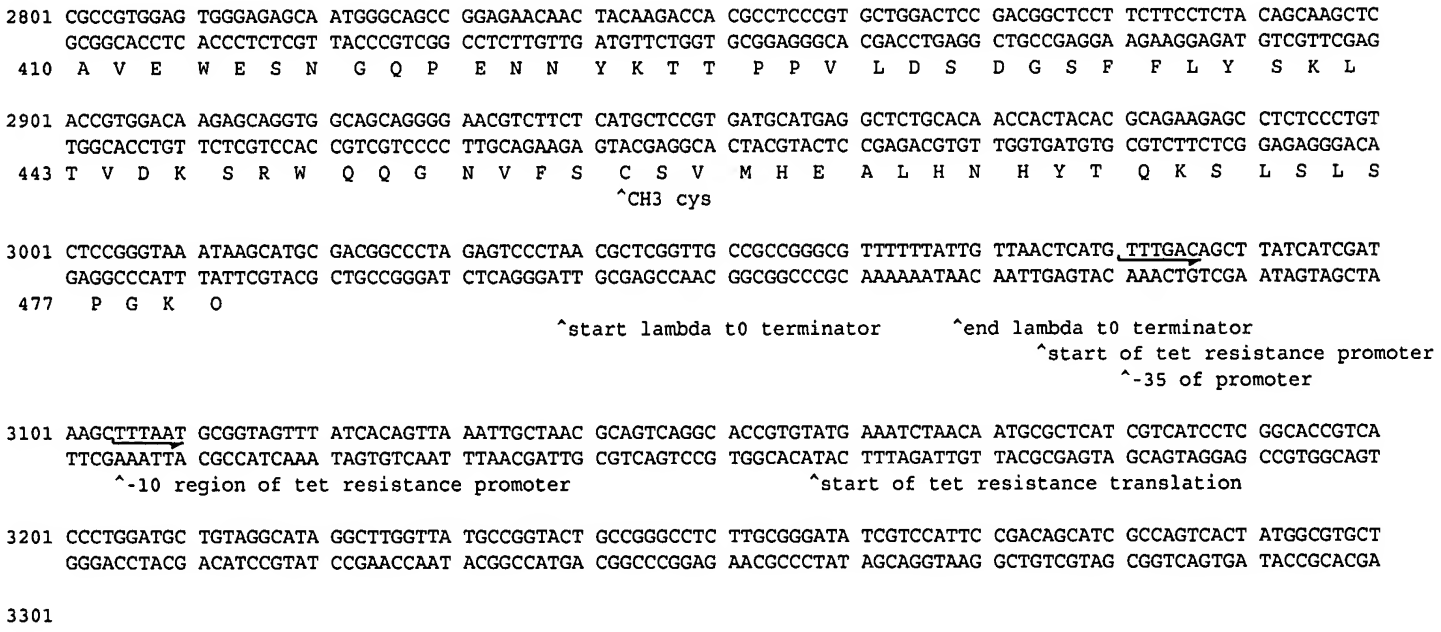
Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
Serial No.: 10/764,428
Sheet 16 of 50

FIG. 15C



Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
Serial No.: 10/764,428
Sheet 17 of 50

FIG. 15D



Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
Serial No.: 10/764,428
Sheet 18 of 50

FIG. 16A

Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
Serial No.: 10/764,428
Sheet 19 of 50

FIG. 16B

```
1001 GGACAGCACC TACAGCCTCA GCAGCACCCT GACGCTGAGC AAAGCAGACT ACGAGAAACA CAAAGTCTAC GCCTGCGAAG TCACCCATCA GGGCCTGAGC
     CCTGTCGTGG ATGTCGGAGT CGTCGTGGGA CTGCGACTCG TTTCGTCTGA TGCTCTTTGT GTTTCAGATG CGGACGCTTC AGTGGGTAGT CCCGGACTCG
 193  D  S  T   Y  S  L  S   S  T  L   T  L  S   K  A  D  Y   E  K  H   K  V  Y   A  C  E  V   T  H  Q   G  L  S

1101 TCGCCCGTCA CAAAGAGCTT CAACAGGGGA GAGTGTTAAT TAAATCCTCT ACGCCGGACG CATCGTGGCG AGCTCGGTAC CCGGGGATCT AGGCCTAACG
     AGCGGGCAGT GTTTCTCGAA GTTGTCCCCT CTCACAATTA ATTTAGGAGA TGCGGCCTGC GTAGCACCGC TCGAGCCATG GGCCCCTAGA TCCGGATTGC
 226  S  P  V  T   K  S  F   N  R  G   E  C  O

1201 CTCGGTTGCC GCCGGGCGTT TTTTATTGTT GCCGACGCGC ATCTCGAATG AACTGTGTGC GCAGGTAGAA GCTTTGGAGA TTATCGTCAC TGCAATGCTT
     GAGCCAACGG CGGCCCGCAA AAAATAACAA CGGCTGCGCG TAGAGCTTAC TTGACACACG CGTCCATCTT CGAAACCTCT AATAGCAGTG ACGTTACGAA

1301 CGCAATATGG CGCAAAATGA CCAACAGCGG TTGATTGATC AGGTAGAGGG GGCGCTGTAC GAGGTAAAGC CCGATGCCAG CATTCCTGAC GACGATACGG
     GCGTTATACC GCGTTTTACT GGTTGTCGCC AACTAACTAG TCCATCTCCC CCGCGACATG CTCCATTTCG GGCTACGGTC GTAAGGACTG CTGCTATGCC

1401 AGCTGCTGCG CGATTACGTA AAGAAGTTAT TGAAGCATCC TCGTCAGTAA AAAGTTAATC TTTTCAACAG CTGTCATAAA GTTGTCACGG CCGAGACTTA
     TCGACGACGC GCTAATGCAT TTCTTCAATA ACTTCGTAGG AGCAGTCATT TTTCAATTAG AAAAGTTGTC GACAGTATTT CAACAGTGCC GGCTCTGAAT

1501 TAGTCGCTTT GTTTTTATTT TTTAATGTAT TTGTAACTAG TACGCAAGTT CACGTAAAAA GGGTATCTAG AATTATGAAG AAGAATATCG CATTTCTTCT
     ATCAGCGAAA CAAAAATAAA AAATTACATA AACATTGATC ATGCGTTCAA GTGCATTTTT CCCATAGATC TTAATACTTC TTCTTATAGC GTAAAGAAGA
   1                                                                                    M  K   K  N  I  A   F  L  L
                                                                                       ^STII Signal TIR-1

1601 TGCATCTATG TTCGTTTTTT CTATTGCTAC AAACGCGTAC GCTGAGGTTC AGCTGGTGGA GTCTGGCGGT GGCCTGGTGC AGCCAGGGGG CTCACTCCGT
     ACGTAGATAC AAGCAAAAAA GATAACGATG TTTGCGCATG CGACTCCAAG TCGACCACCT CAGACCGCCA CCGGACCACG TCGGTCCCCC GAGTGAGGCA
  10  A  S  M   F  V  F  S   I  A  T   N  A  Y   A  E  V  Q   L  V  E   S  G  G   G  L  V  Q   P  G  G   S  L  R
                                                 ^Anti-VEGF Heavy Chain (version Y0317)

1701 TTGTCCTGTG CAGCTTCTGG CTACGACTTC ACGCACTACG GTATGAACTG GGTCCGTCAG GCCCCGGGTA AGGGCCTGGA ATGGGTTGGA TGGATTAACA
     AACAGGACAC GTCGAAGACC GATGCTGAAG TGCGTGATGC CATACTTGAC CCAGGCAGTC CGGGGCCCAT TCCCGGACCT TACCCAACCT ACCTAATTGT
  43  L  S  C  A   A  S  G   Y  D  F   T  H  Y  G   M  N  W   V  R  Q   A  P  G  K   G  L  E   W  V  G   W  I  N  T

1801 CCTATACCGG TGAACCGACC TATGCTGCGG ATTTCAAACG TCGTTTCACT TTTTCTTTAG ACACCTCCAA AAGCACAGCA TACCTGCAGA TGAACAGCCT
     GGATATGGCC ACTTGGCTGG ATACGACGCC TAAAGTTTGC AGCAAAGTGA AAAAGAAATC TGTGGAGGTT TTCGTGTCGT ATGGACGTCT ACTTGTCGGA
  77   Y  T  G   E  P  T   Y  A  A  D   F  K  R   R  F  T   F  S  L  D   T  S  K   S  T  A   Y  L  Q  M   N  S  L

1901 GCGCGCTGAG GACACTGCCG TCTATTACTG TGCAAAGTAC CCGTACTATT ATGGGACGAG CCACTGGTAT TTCGACGTCT GGGGTCAAGG AACCCTGGTC
     CGCGCGACTC CTGTGACGGC AGATAATGAC ACGTTTCATG GGCATGATAA TACCCTGCTC GGTGACCATA AAGCTGCAGA CCCCAGTTCC TTGGGACCAG
 110  R  A  E   D  T  A  V   Y  Y  C   A  K  Y   P  Y  Y  Y   G  T  S   H  W  Y   F  D  V  W   G  Q  G   T  L  V

2001 ACCGTCTCCT CGGCCTCCAC CAAGGGCCCA TCGGTCTTCC CCCTGGCACC CTCCTCCAAG AGCACCTCTG GGGGCACAGC GGCCCTGGGC TGCCTGGTCA
     TGGCAGAGGA GCCGGAGGTG GTTCCCGGGT AGCCAGAAGG GGGACCGTGG GAGGAGGTTC TCGTGGAGAC CCCCGTGTCG CCGGGACCCG ACGGACCAGT
 143  T  V  S  S   A  S  T   K  G  P   S  V  F  P   L  A  P   S  S  K   S  T  S  G   G  T  A   A  L  G   C  L  V  K
```

Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
Serial No.: 10/764,428
Sheet 20 of 50

FIG. 16C

```
2101 AGGACTACTT CCCCGAACCG GTGACGGTGT CGTGGAACTC AGGCGCCCTG ACCAGCGGCG TGCACACCTT CCCGGCTGTC CTACAGTCCT CAGGACTCTA
     TCCTGATGAA GGGGCTTGGC CACTGCCACA GCACCTTGAG TCCGCGGGAC TGGTCGCCGC ACGTGTGGAA GGGCCGACAG GATGTCAGGA GTCCTGAGAT
 177   D  Y  F   P  E  P   V  T  V  S   W  N  S   G  A  L   T  S  G  V   H  T  F   P  A  V   L  Q  S  S   G  L  Y

2201 CTCCCTCAGC AGCGTGGTGA CTGTGCCCTC TAGCAGCTTG GGCACCCAGA CCTACATCTG CAACGTGAAT CACAAGCCCA GCAACACCAA GGTGGACAAG
     GAGGGAGTCG TCGCACCACT GACACGGGAG ATCGTCGAAC CCGTGGGTCT GGATGTAGAC GTTGCACTTA GTGTTCGGGT CGTTGTGGTT CCACCTGTTC
 210   S  L  S   S  V  V  T   V  P  S   S  S  L   G  T  Q  T   Y  I  C   N  V  N   H  K  P  S   N  T  K   V  D  K

2301 AAAGTTGAGC CCAAATCTTG TGACAAAACT CACACATGCC CACCGTGCCC AGCACCTGAA CTCCTGGGGG GACCGTCAGT CTTCCTCTTC CCCCCAAAAC
     TTTCAACTCG GGTTTAGAAC ACTGTTTTGA GTGTGTACGG GTGGCACGGG TCGTGGACTT GAGGACCCCC CTGGCAGTCA GAAGGAGAAG GGGGGTTTTG
 243 K  V  E  P   K  S  C   D  K  T   H  T  C  P   P  C  P   A  P  E   L  L  G  G   P  S  V   F  L  F   P  P  K  P

2401 CCAAGGACAC CCTCATGATC TCCCGGACCC CTGAGGTCAC ATGCGTGGTG GTGGACGTGA GCCACGAAGA CCCTGAGGTC AAGTTCAACT GGTACGTGGA
     GGTTCCTGTG GGAGTACTAG AGGGCCTGGG GACTCCAGTG TACGCACCAC CACCTGCACT CGGTGCTTCT GGGACTCCAG TTCAAGTTGA CCATGCACCT
 277   K  D  T   L  M  I   S  R  T  P   E  V  T   C  V  V   V  D  V  S   H  E  D   P  E  V   K  F  N  W   Y  V  D

2501 CGGCGTGGAG GTGCATAATG CCAAGACAAA GCCGCGGGAG GAGCAGTACA ACAGCACGTA CCGTGTGGTC AGCGTCCTCA CCGTCCTGCA CCAGGACTGG
     GCCGCACCTC CACGTATTAC GGTTCTGTTT CGGCGCCCTC CTCGTCATGT TGTCGTGCAT GGCACACCAG TCGCAGGAGT GGCAGGACGT GGTCCTGACC
 310   G  V  E   V  H  N  A   K  T  K   P  R  E   E  Q  Y  N   S  T  Y   R  V  V   S  V  L  T   V  L  H   Q  D  W

2601 CTGAATGGCA AGGAGTACAA GTGCAAGGTC TCCAACAAAG CCCTCCCAGC CCCCATCGAG AAAACCATCT CCAAAGCCAA AGGGCAGCCC CGAGAACCAC
     GACTTACCGT TCCTCATGTT CACGTTCCAG AGGTTGTTTC GGGAGGGTCG GGGGTAGCTC TTTTGGTAGA GGTTTCGGTT TCCCGTCGGG GCTCTTGGTG
 343 L  N  G  K   E  Y  K   C  K  V   S  N  K  A   L  P  A   P  I  E   K  T  I  S   K  A  K   G  Q  P   R  E  P  Q

2701 AGGTGTACAC CCTGCCCCCA TCCCGGGAAG AGATGACCAA GAACCAGGTC AGCCTGACCT GCCTGGTCAA AGGCTTCTAT CCCAGCGACA TCGCCGTGGA
     TCCACATGTG GGACGGGGGT AGGGCCCTTC TCTACTGGTT CTTGGTCCAG TCGGACTGGA CGGACCAGTT TCCGAAGATA GGGTCGCTGT AGCGGCACCT
 377   V  Y  T   L  P  P   S  R  E  E   M  T  K   N  Q  V   S  L  T  C   L  V  K   G  F  Y   P  S  D  I   A  V  E

2801 GTGGGAGAGC AATGGGCAGC CGGAGAACAA CTACAAGACC ACGCCTCCCG TGCTGGACTC CGACGGCTCC TTCTTCCTCT ACAGCAAGCT CACCGTGGAC
     CACCCTCTCG TTACCCGTCG GCCTCTTGTT GATGTTCTGG TGCGGAGGGC ACGACCTGAG GCTGCCGAGG AAGAAGGAGA TGTCGTTCGA GTGGCACCTG
 410   W  E  S   N  G  Q  P   E  N  N   Y  K  T   T  P  P  V   L  D  S   D  G  S   F  F  L  Y   S  K  L   T  V  D

2901 AAGAGCAGGT GGCAGCAGGG GAACGTCTTC TCATGCTCCG TGATGCATGA GGCTCTGCAC AACCACTACA CGCAGAAGAG CCTCTCCCTG TCTCCGGGTA
     TTCTCGTCCA CCGTCGTCCC CTTGCAGAAG AGTACGAGGC ACTACGTACT CCGAGACGTG TTGGTGATGT GCGTCTTCTC GGAGAGGGAC AGAGGCCCAT
 443 K  S  R  W   Q  Q  G   N  V  F   S  C  S  V   M  H  E   A  L  H   N  H  Y  T   Q  K  S   L  S  L   S  P  G  K

3001 AATAAGCATG CGACGGCCCT AGAGTCCCTA ACGCTCGGTT GCCGCCGGGC GTTTTTTATT GTTAACTCAT GTTTGACAGC TTATCATCGA TAAGCTTTAA
     TTATTCGTAC GCTGCCGGGA TCTCAGGGAT TGCGAGCCAA CGGCGGCCCG CAAAAAATAA CAATTGAGTA CAAACTGTCG AATAGTAGCT ATTCGAAATT
 477   O

3101 TGCGGTAGTT TATCACAGTT AAATTGCTAA CGCAGTCAGG CACCGTGTAT GAAATCTAAC AATGCGCTCA TCGTCATCCT CGGCACCGTC ACCCTGGATG
     ACGCCATCAA ATAGTGTCAA TTTAACGATT GCGTCAGTCC GTGGCACATA CTTTAGATTG TTACGCGAGT AGCAGTAGGA GCCGTGGCAG TGGGACCTAC
                                                                                  ^Start Tet Resistance Coding Sequence
```

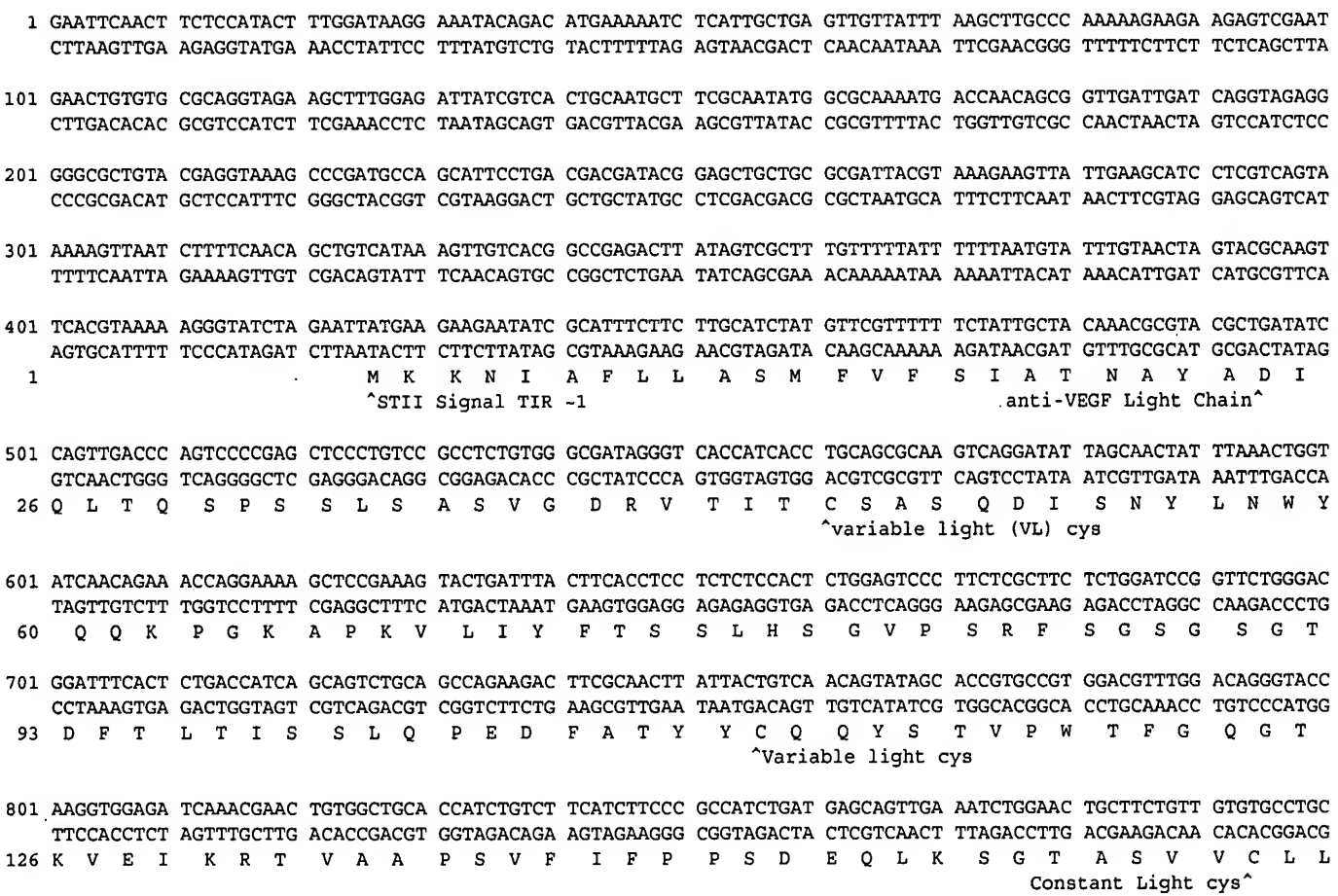
FIG. 16D

```
3201 CTGTAGGCAT AGGCTTGGTT ATGCCGGTAC TGCCGGGCCT CTTGCGGGAT ATCGTCCATT CCGACAGCAT CGCCAGTCAC TATGGCGTGC TGCTAGCGCT
     GACATCCGTA TCCGAACCAA TACGGCCATG ACGGCCCGGA GAACGCCCTA TAGCAGGTAA GGCTGTCGTA GCGGTCAGTG ATACCGCACG ACGATCGCGA

3301
```

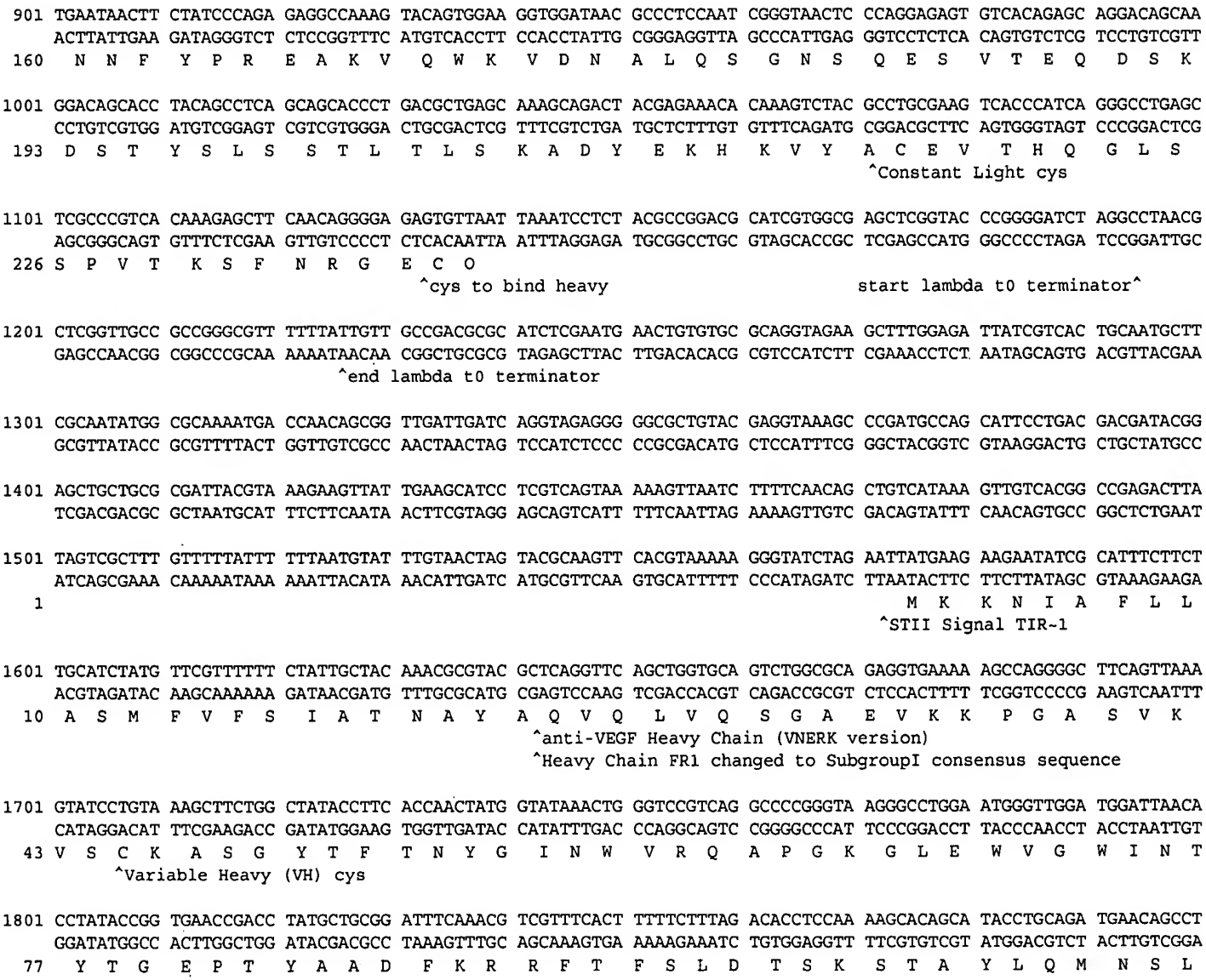
Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
Serial No.: 10/764,428
Sheet 22 of 50

FIG. 17A



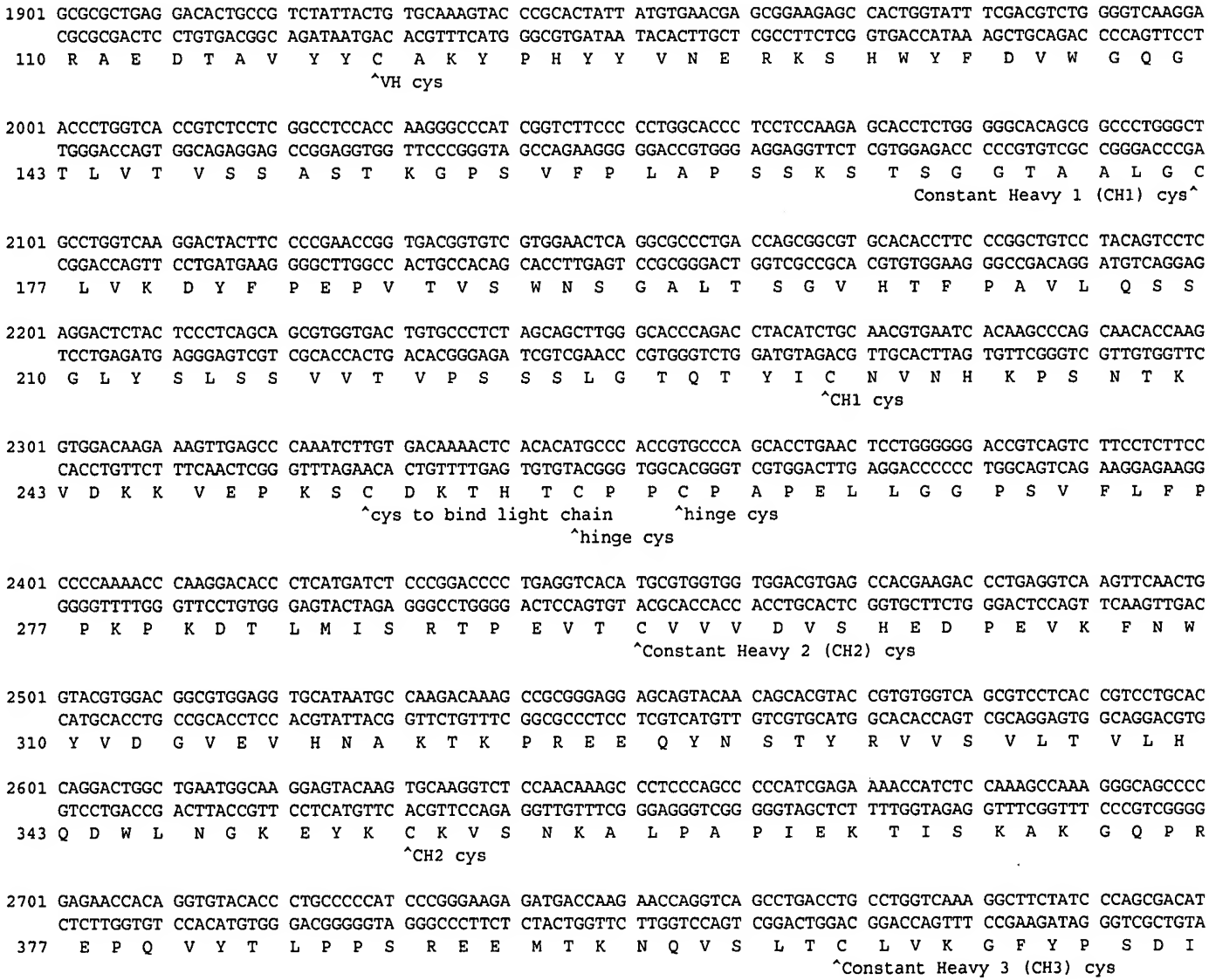
Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
Serial No.: 10/764,428
Sheet 23 of 50

FIG. 17B



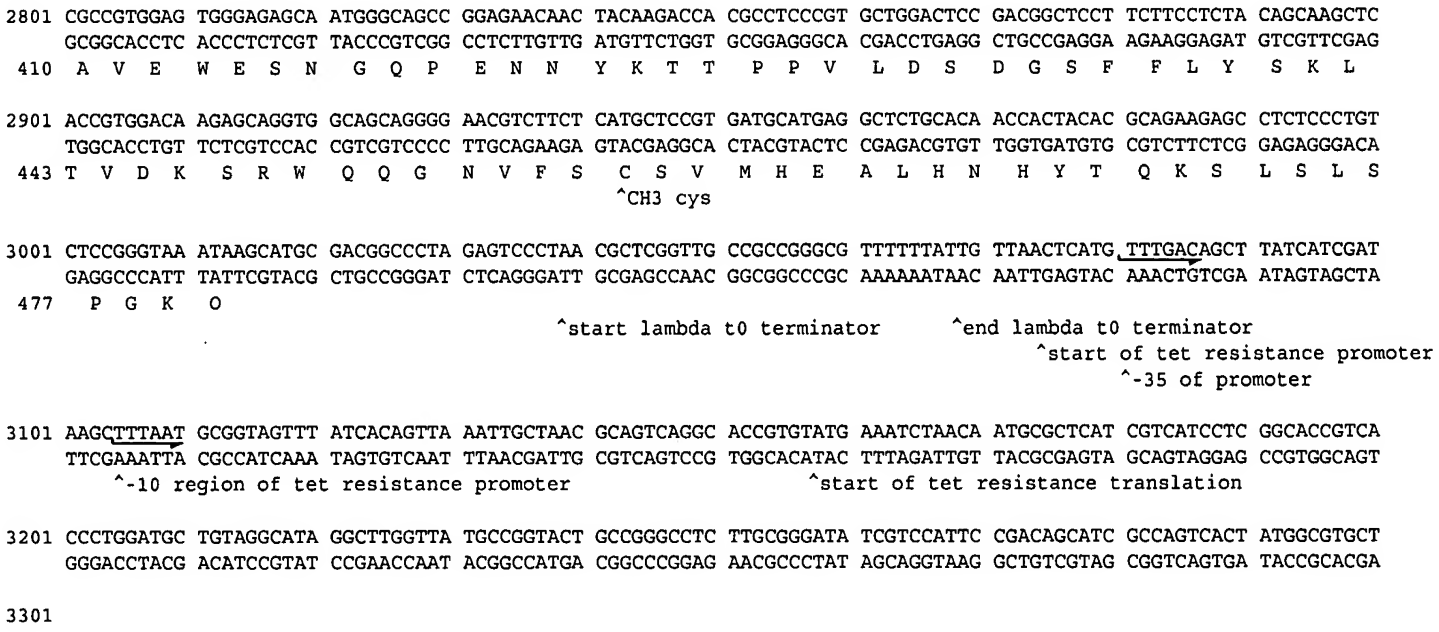
Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
Serial No.: 10/764,428
Sheet 24 of 50

FIG. 17C



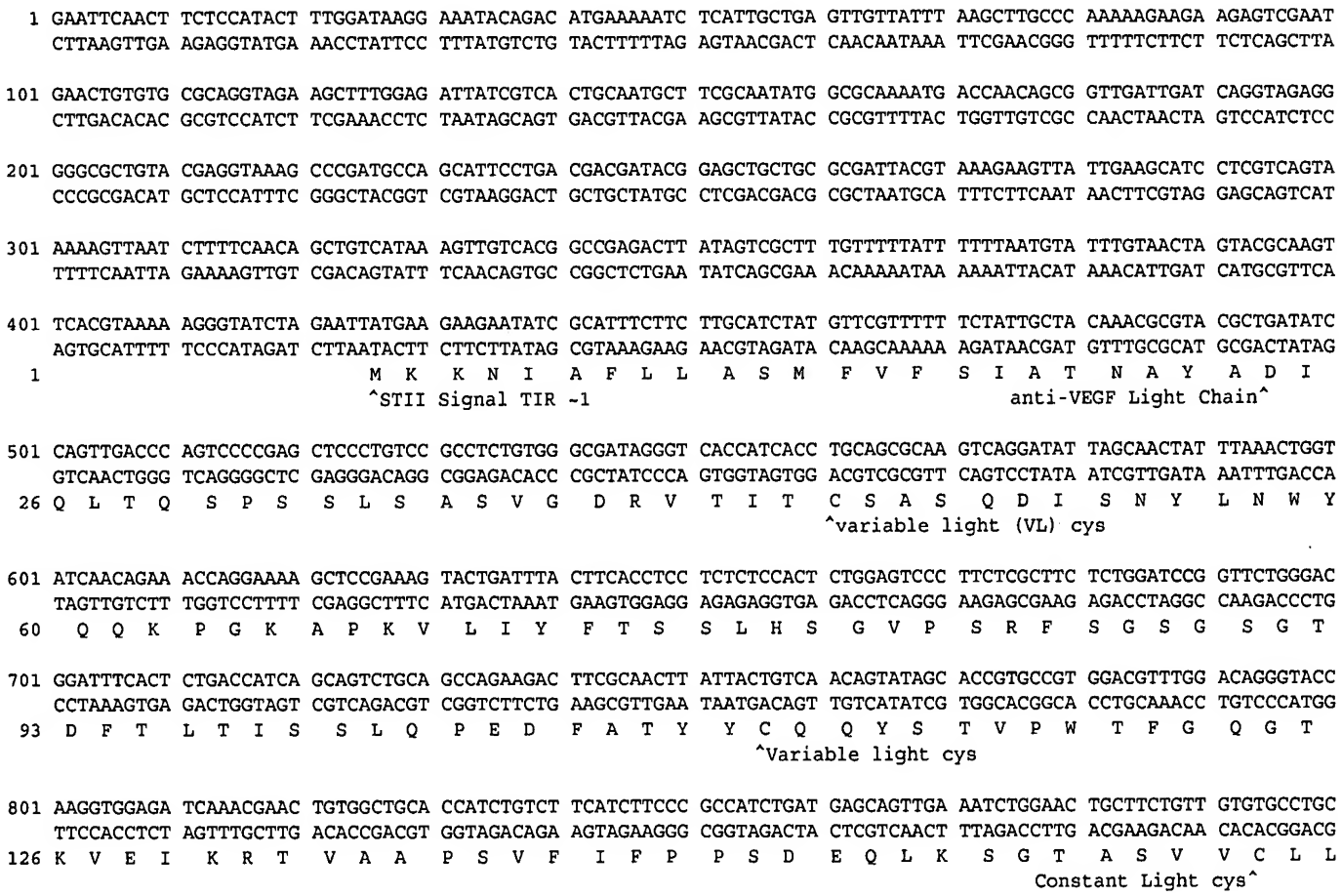
Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
Serial No.: 10/764,428
Sheet 25 of 50

FIG. 17D



Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
Serial No.: 10/764,428
Sheet 26 of 50

FIG. 18A



Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
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FIG. 18B

```
 901 TGAATAACTT CTATCCCAGA GAGGCCAAAG TACAGTGGAA GGTGGATAAC GCCCTCCAAT CGGGTAACTC CCAGGAGAGT GTCACAGAGC AGGACAGCAA
     ACTTATTGAA GATAGGGTCT CTCCGGTTTC ATGTCACCTT CCACCTATTG CGGGAGGTTA GCCCATTGAG GGTCCTCTCA CAGTGTCTCG TCCTGTCGTT
 160   N  N  F   Y  P  R   E  A  K  V   Q  W  K   V  D  N   A  L  Q  S   G  N  S   Q  E  S   V  T  E  Q   D  S  K

1001 GGACAGCACC TACAGCCTCA GCAGCACCCT GACGCTGAGC AAAGCAGACT ACGAGAAACA CAAAGTCTAC GCCTGCGAAG TCACCCATCA GGGCCTGAGC
     CCTGTCGTGG ATGTCGGAGT CGTCGTGGGA CTGCGACTCG TTTCGTCTGA TGCTCTTTGT GTTTCAGATG CGGACGCTTC AGTGGGTAGT CCCGGACTCG
 193  D  S  T   Y  S  L  S   S  T  L   T  L  S   K  A  D  Y   E  K  H   K  V  Y   A  C  E  V   T  H  Q   G  L  S
                                                                                    ^Constant Light cys

1101 TCGCCCGTCA CAAAGAGCTT CAACAGGGGA GAGTGTTAAT TAAATCCTCT ACGCCGGACG CATCGTGGCG AGCTCGGTAC CCGGGGATCT AGGCCTAACG
     AGCGGGCAGT GTTTCTCGAA GTTGTCCCCT CTCACAATTA ATTTAGGAGA TGCGGCCTGC GTAGCACCGC TCGAGCCATG GGCCCCTAGA TCCGGATTGC
 226 S  P  V  T   K  S  F   N  R  G   E  C  O
                                  ^cys to bind heavy                          start lambda t0 terminator^

1201 CTCGGTTGCC GCCGGGCGTT TTTTATTGTT GCCGACGCGC ATCTCGAATG AACTGTGTGC GCAGGTAGAA GCTTTGGAGA TTATCGTCAC TGCAATGCTT
     GAGCCAACGG CGGCCCGCAA AAAATAACAA CGGCTGCGCG TAGAGCTTAC TTGACACACG CGTCCATCTT CGAAACCTCT AATAGCAGTG ACGTTACGAA
                              ^end lambda t0 terminator

1301 CGCAATATGG CGCAAAATGA CCAACAGCGG TTGATTGATC AGGTAGAGGG GGCGCTGTAC GAGGTAAAGC CCGATGCCAG CATTCCTGAC GACGATACGG
     GCGTTATACC GCGTTTTACT GGTTGTCGCC AACTAACTAG TCCATCTCCC CCGCGACATG CTCCATTTCG GGCTACGGTC GTAAGGACTG CTGCTATGCC

1401 AGCTGCTGCG CGATTACGTA AAGAAGTTAT TGAAGCATCC TCGTCAGTAA AAAGTTAATC TTTTCAACAG CTGTCATAAA GTTGTCACGG CCGAGACTTA
     TCGACGACGC GCTAATGCAT TTCTTCAATA ACTTCGTAGG AGCAGTCATT TTTCAATTAG AAAAGTTGTC GACAGTATTT CAACAGTGCC GGCTCTGAAT

1501 TAGTCGCTTT GTTTTTATTT TTTAATGTAT TTGTAACTAG TACGCAAGTT CACGTAAAAA GGGTATCTAG AATTATGAAG AAGAATATCG CATTTCTTCT
     ATCAGCGAAA CAAAAATAAA AAATTACATA AACATTGATC ATGCGTTCAA GTGCATTTTT CCCATAGATC TTAATACTTC TTCTTATAGC GTAAAGAAGA
   1                                                                                    M  K  K  N  I  A   F  L  L
                                                                                        ^STII Signal TIR-1

1601 TGCATCTATG TTCGTTTTTT CTATTGCTAC AAACGCGTAC GCTCAGGTTC AGCTGCAAGA GTCTGGCCCG GGCCTGGTGA AACCATCTCA GACTCTCTCC
     ACGTAGATAC AAGCAAAAAA GATAACGATG TTTGCGCATG CGAGTCCAAG TCGACGTTCT CAGACCGGGC CCGGACCACT TTGGTAGAGT CTGAGAGAGG
  10  A  S  M   F  V  F  S   I  A  T   N  A  Y   A  Q  V  Q   L  Q  E   S  G  P   G  L  V  K   P  S  Q   T  L  S
                                                  ^anti-VEGF heavy chain (VNERK version)
                                                  ^Heavy chain FR1 changed to Subgroup II consensus sequence

1701 TTGACTTGTA CTGTTTCTGG CTATACCTTC ACCAACTATG GTATAAACTG GGTCCGTCAG GCCCCGGGTA AGGGCCTGGA ATGGGTTGGA TGGATTAACA
     AACTGAACAT GACAAAGACC GATATGGAAG TGGTTGATAC CATATTTGAC CCAGGCAGTC CGGGGCCCAT TCCCGGACCT TACCCAACCT ACCTAATTGT
  43 L  T  C  T   V  S  G   Y  T  F   T  N  Y  G   I  N  W   V  R  Q   A  P  G  K   G  L  E   W  V  G   W  I  N  T
        ^Variable Heavy (VH) cys

1801 CCTATACCGG TGAACCGACC TATGCTGCGG ATTTCAAACG TCGTTTCACT TTTTCTTTAG ACACCTCCAA AAGCACAGCA TACCTGCAGA TGAACAGCCT
     GGATATGGCC ACTTGGCTGG ATACGACGCC TAAAGTTTGC AGCAAAGTGA AAAAGAAATC TGTGGAGGTT TTCGTGTCGT ATGGACGTCT ACTTGTCGGA
  77   Y  T  G   E  P  T   Y  A  A  D   F  K  R   R  F  T   F  S  L  D   T  S  K   S  T  A   Y  L  Q  M   N  S  L
```

Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
Serial No.: 10/764,428
Sheet 28 of 50

FIG. 18C

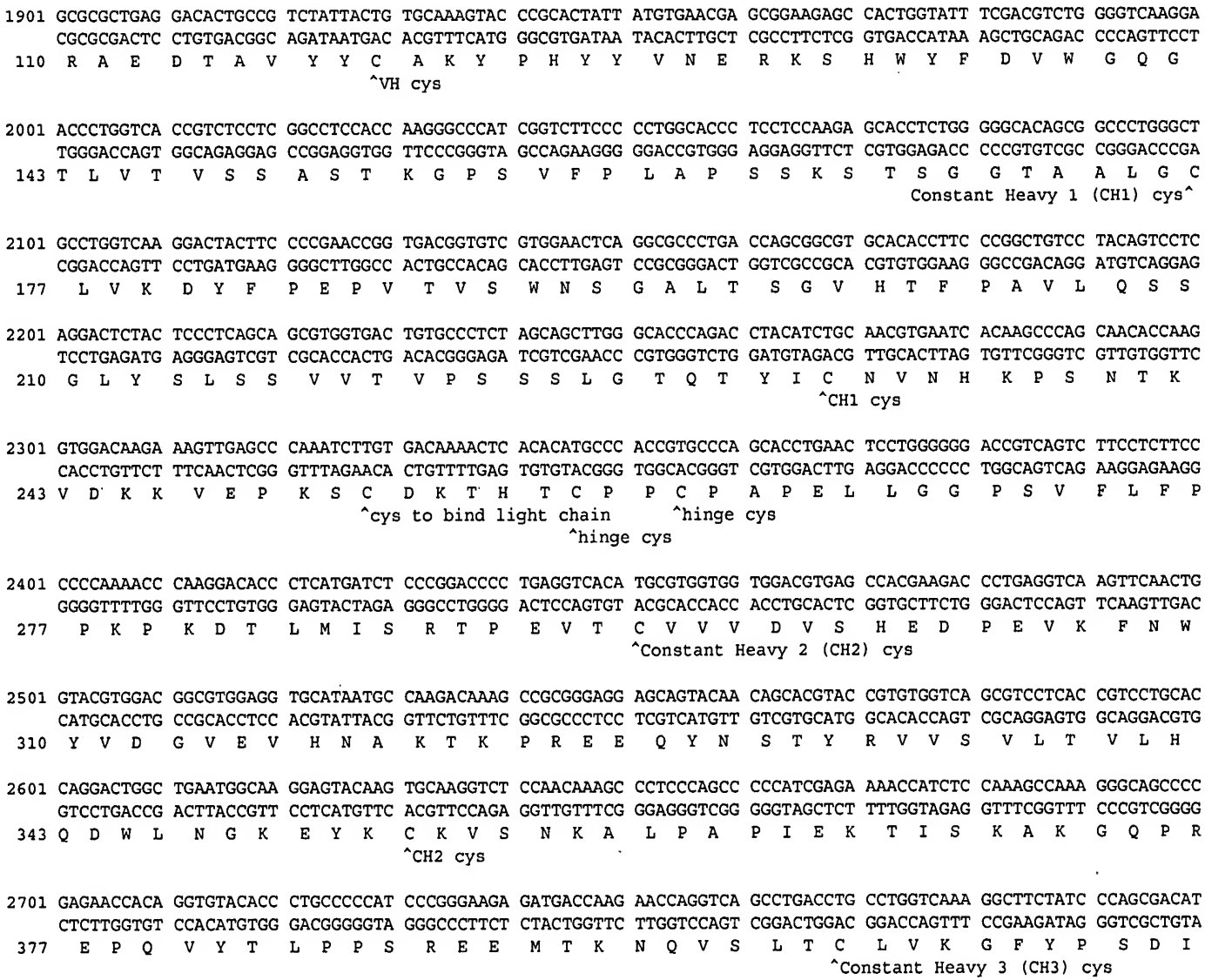
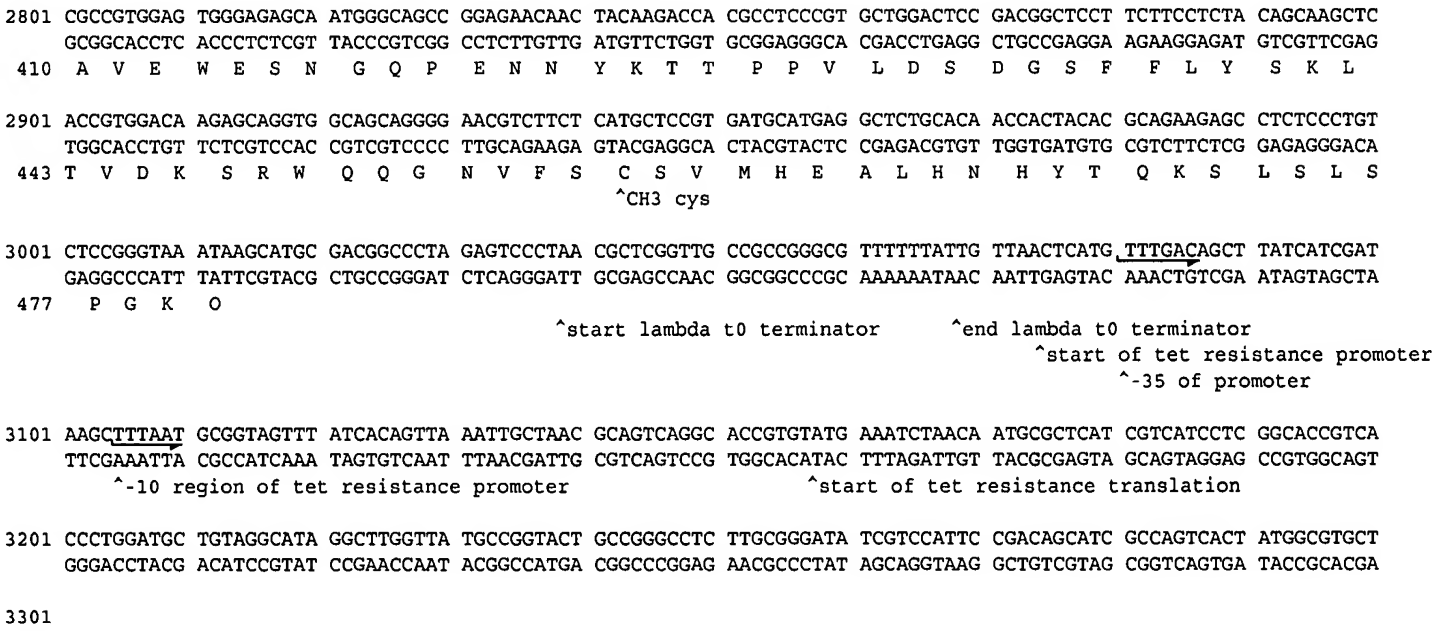

1901 GCGCGCTGAG GACACTGCCG TCTATTACTG TGCAAAGTAC CCGCACTATT ATGTGAACGA GCGGAAGAGC CACTGGTATT TCGACGTCTG GGGTCAAGGA
CGCGCGACTC CTGTGACGGC AGATAATGAC ACGTTTCATG GGCGTGATAA TACACTTGCT CGCCTTCTCG GTGACCATAA AGCTGCAGAC CCCAGTTCCT
110 R A E D T A V Y Y C A K Y P H Y Y V N E R K S H W Y F D V W G Q G
^VH cys
2001 ACCCTGGTCA CCGTCTCCTC GGCCTCCACC AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG GCCCTGGGCT
TGGGACCAGT GGCAGAGGAG CCGGAGGTGG TTCCCGGGTA GCCAGAAGGG GGACCGTGGG AGGAGGTTCT CGTGGAGACC CCCGTGTCGC CGGGACCCGA
143 T L V T V S S A S T K G P S V F P L A P S S K S T S G G T A A L G C
Constant Heavy 1 (CH1) cys^
2101 GCCTGGTCAA GGACTACTTC CCCGAACCGG TGACGGTGTC GTGGAACTCA GGCGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCCTC
CGGACCAGTT CCTGATGAAG GGGCTTGGCC ACTGCCACAG CACCTTGAGT CCGCGGGACT GGTCGCCGCA CGTGTGGAAG GGCCGACAGG ATGTCAGGAG
177 L V K D Y F P E P V T V S W N S G A L T S G V H T F P A V L Q S S
2201 AGGACTCTAC TCCCTCAGCA GCGTGGTGAC TGTGCCCTCT AGCAGCTTGG GCACCCAGAC CTACATCTGC AACGTGAATC ACAAGCCCAG CAACACCAAG
TCCTGAGATG AGGGAGTCGT CGCACCACTG ACACGGGAGA TCGTCGAACC CGTGGGTCTG GATGTAGACG TTGCACTTAG TGTTCGGGTC GTTGTGGTTC
210 G L Y S L S S V V T V P S S S L G T Q T Y I C N V N H K P S N T K
^CH1 cys
2301 GTGGACAAGA AAGTTGAGCC CAAATCTTGT GACAAAACTC ACACATGCCC ACCGTGCCCA GCACCTGAAC TCCTGGGGGG ACCGTCAGTC TTCCTCTTCC
CACCTGTTCT TTCAACTCGG GTTTAGAACA CTGTTTTGAG TGTGTACGGG TGGCACGGGT CGTGGACTTG AGGACCCCCC TGGCAGTCAG AAGGAGAAGG
243 V D K K V E P K S C D K T H T C P P C P A P E L L G G P S V F L F P
^cys to bind light chain ^hinge cys
^hinge cys
2401 CCCCAAAACC CAAGGACACC CTCATGATCT CCCGGACCCC TGAGGTCACA TGCGTGGTGG TGGACGTGAG CCACGAAGAC CCTGAGGTCA AGTTCAACTG
GGGGTTTTGG GTTCCTGTGG GAGTACTAGA GGGCCTGGGG ACTCCAGTGT ACGCACCACC ACCTGCACTC GGTGCTTCTG GGACTCCAGT TCAAGTTGAC
277 P K P K D T L M I S R T P E V T C V V V D V S H E D P E V K F N W
^Constant Heavy 2 (CH2) cys
2501 GTACGTGGAC GGCGTGGAGG TGCATAATGC CAAGACAAAG CCGCGGGAGG AGCAGTACAA CAGCACGTAC CGTGTGGTCA GCGTCCTCAC CGTCCTGCAC
CATGCACCTG CCGCACCTCC ACGTATTACG GTTCTGTTTC GGCGCCCTCC TCGTCATGTT GTCGTGCATG GCACACCAGT CGCAGGAGTG GCAGGACGTG
310 Y V D G V E V H N A K T K P R E E Q Y N S T Y R V V S V L T V L H
2601 CAGGACTGGC TGAATGGCAA GGAGTACAAG TGCAAGGTCT CCAACAAAGC CCTCCCAGCC CCCATCGAGA AAACCATCTC CAAAGCCAAA GGGCAGCCCC
GTCCTGACCG ACTTACCGTT CCTCATGTTC ACGTTCCAGA GGTTGTTTCG GGAGGGTCGG GGGTAGCTCT TTTGGTAGAG GTTTCGGTTT CCCGTCGGGG
343 Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K A K G Q P R
^CH2 cys
2701 GAGAACCACA GGTGTACACC CTGCCCCCAT CCCGGGAAGA GATGACCAAG AACCAGGTCA GCCTGACCTG CCTGGTCAAA GGCTTCTATC CCAGCGACAT
CTCTTGGTGT CCACATGTGG GACGGGGGTA GGGCCCTTCT CTACTGGTTC TTGGTCCAGT CGGACTGGAC GGACCAGTTT CCGAAGATAG GGTCGCTGTA
377 E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P S D I
^Constant Heavy 3 (CH3) cys

FIG. 18D



Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
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FIG. 19A

Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
Serial No.: 10/764,428
Sheet 31 of 50

FIG. 19B

```
1001 GGACAGCACC TACAGCCTCA GCAGCACCCT GACGCTGAGC AAAGCAGACT ACGAGAAACA CAAAGTCTAC GCCTGCGAAG TCACCCATCA GGGCCTGAGC
     CCTGTCGTGG ATGTCGGAGT CGTCGTGGGA CTGCGACTCG TTTCGTCTGA TGCTCTTTGT GTTTCAGATG CGGACGCTTC AGTGGGTAGT CCCGGACTCG
 193  D  S  T   Y  S  L  S   S  T  L   T  L  S   K  A  D  Y   E  K  H   K  V  Y   A  C  E  V   T  H  Q   G  L  S

1101 TCGCCCGTCA CAAAGAGCTT CAACAGGGGA GAGTGTTAAT TAAATCCTCT ACGCCGGACG CATCGTGGCG AGCTCGGTAC CCGGGGATCT AGGCCTAACG
     AGCGGGCAGT GTTTCTCGAA GTTGTCCCCT CTCACAATTA ATTTAGGAGA TGCGGCCTGC GTAGCACCGC TCGAGCCATG GGCCCCTAGA TCCGGATTGC
 226 S  P  V  T   K  S  F   N  R  G   E  C  O

1201 CTCGGTTGCC GCCGGGCGTT TTTTATTGTT GCCGACGCGC ATCTCGAATG AACTGTGTGC GCAGGTAGAA GCTTTGGAGA TTATCGTCAC TGCAATGCTT
     GAGCCAACGG CGGCCCGCAA AAAATAACAA CGGCTGCGCG TAGAGCTTAC TTGACACACG CGTCCATCTT CGAAACCTCT AATAGCAGTG ACGTTACGAA

1301 CGCAATATGG CGCAAAATGA CCAACAGCGG TTGATTGATC AGGTAGAGGG GGCGCTGTAC GAGGTAAAGC CCGATGCCAG CATTCCTGAC GACGATACGG
     GCGTTATACC GCGTTTTACT GGTTGTCGCC AACTAACTAG TCCATCTCCC CCGCGACATG CTCCATTTCG GGCTACGGTC GTAAGGACTG CTGCTATGCC

1401 AGCTGCTGCG CGATTACGTA AAGAAGTTAT TGAAGCATCC TCGTCAGTAA AAAGTTAATC TTTTCAACAG CTGTCATAAA GTTGTCACGG CCGAGACTTA
     TCGACGACGC GCTAATGCAT TTCTTCAATA ACTTCGTAGG AGCAGTCATT TTTCAATTAG AAAAGTTGTC GACAGTATTT CAACAGTGCC GGCTCTGAAT

1501 TAGTCGCTTT GTTTTTATTT TTTAATGTAT TTGTAACTAG TACGCAAGTT CACGTAAAAA GGGTATCTAG AATTATGAAG AAGAATATCG CATTTCTTCT
     ATCAGCGAAA CAAAAATAAA AAATTACATA AACATTGATC ATGCGTTCAA GTGCATTTTT CCCATAGATC TTAATACTTC TTCTTATAGC GTAAAGAAGA
   1                                                                                    M  K   K  N  I  A   F  L  L
                                                                                       ^STII Signal TIR-1

1601 TGCATCTATG TTCGTTTTTT CTATTGCTAC AAACGCGTAC GCTCAGGTTC AGCTGGTGCA GTCTGGCGCA GAGGTGAAAA AGCCAGGGGC TTCAGTTAAA
     ACGTAGATAC AAGCAAAAAA GATAACGATG TTTGCGCATG CGAGTCCAAG TCGACCACGT CAGACCGCGT CTCCACTTTT TCGGTCCCCG AAGTCAATTT
  10  A  S  M   F  V  F  S   I  A  T   N  A  Y   A  Q  V  Q   L  V  Q   S  G  A   E  V  K  K   P  G  A   S  V  K
                                                 ^Anti-VEGF (version Y0317) Heavy Chain
                                                 ^Heavy Chain FR1 changed to SubgroupI consensus sequence

1701 GTATCCTGTA AAGCTTCTGG CTACGACTTC ACGCACTACG GTATGAACTG GGTCCGTCAG GCCCCGGGTA AGGGCCTGGA ATGGGTTGGA TGGATTAACA
     CATAGGACAT TTCGAAGACC GATGCTGAAG TGCGTGATGC CATACTTGAC CCAGGCAGTC CGGGGCCCAT TCCCGGACCT TACCCAACCT ACCTAATTGT
  43 V  S  C  K   A  S  G   Y  D  F   T  H  Y  G   M  N  W   V  R  Q   A  P  G  K   G  L  E   W  V  G   W  I  N  T

1801 CCTATACCGG TGAACCGACC TATGCTGCGG ATTTCAAACG TCGTTTCACT TTTTCTTTAG ACACCTCCAA AAGCACAGCA TACCTGCAGA TGAACAGCCT
     GGATATGGCC ACTTGGCTGG ATACGACGCC TAAAGTTTGC AGCAAAGTGA AAAAGAAATC TGTGGAGGTT TTCGTGTCGT ATGGACGTCT ACTTGTCGGA
  77   Y  T  G   E  P  T   Y  A  A  D   F  K  R   R  F  T   F  S  L  D   T  S  K   S  T  A   Y  L  Q  M   N  S  L

1901 GCGCGCTGAG GACACTGCCG TCTATTACTG TGCAAAGTAC CCGTACTATT ATGGGACGAG CCACTGGTAT TTCGACGTCT GGGGTCAAGG AACCCTGGTC
     CGCGCGACTC CTGTGACGGC AGATAATGAC ACGTTTCATG GGCATGATAA TACCCTGCTC GGTGACCATA AAGCTGCAGA CCCCAGTTCC TTGGGACCAG
 110  R  A  E   D  T  A  V   Y  Y  C   A  K  Y   P  Y  Y  Y   G  T  S   H  W  Y   F  D  V  W   G  Q  G   T  L  V

2001 ACCGTCTCCT CGGCCTCCAC CAAGGGCCCA TCGGTCTTCC CCCTGGCACC CTCCTCCAAG AGCACCTCTG GGGGCACAGC GGCCCTGGGC TGCCTGGTCA
     TGGCAGAGGA GCCGGAGGTG GTTCCCGGGT AGCCAGAAGG GGGACCGTGG GAGGAGGTTC TCGTGGAGAC CCCCGTGTCG CCGGGACCCG ACGGACCAGT
 143 T  V  S  S   A  S  T   K  G  P   S  V  F  P   L  A  P   S  S  K   S  T  S  G   G  T  A   A  L  G   C  L  V  K
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Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
Serial No.: 10/764,428
Sheet 32 of 50

FIG. 19C

```
2101 AGGACTACTT CCCCGAACCG GTGACGGTGT CGTGGAACTC AGGCGCCCTG ACCAGCGGCG TGCACACCTT CCCGGCTGTC CTACAGTCCT CAGGACTCTA
     TCCTGATGAA GGGGCTTGGC CACTGCCACA GCACCTTGAG TCCGCGGGAC TGGTCGCCGC ACGTGTGGAA GGGCCGACAG GATGTCAGGA GTCCTGAGAT
 177   D  Y  F   P  E  P   V  T  V  S   W  N  S   G  A  L   T  S  G  V   H  T  F   P  A  V   L  Q  S  S   G  L  Y

2201 CTCCCTCAGC AGCGTGGTGA CTGTGCCCTC TAGCAGCTTG GGCACCCAGA CCTACATCTG CAACGTGAAT CACAAGCCCA GCAACACCAA GGTGGACAAG
     GAGGGAGTCG TCGCACCACT GACACGGGAG ATCGTCGAAC CCGTGGGTCT GGATGTAGAC GTTGCACTTA GTGTTCGGGT CGTTGTGGTT CCACCTGTTC
 210   S  L  S   S  V  V  T   V  P  S   S  S  L   G  T  Q  T   Y  I  C   N  V  N   H  K  P  S   N  T  K   V  D  K

2301 AAAGTTGAGC CCAAATCTTG TGACAAAACT CACACATGCC CACCGTGCCC AGCACCTGAA CTCCTGGGGG GACCGTCAGT CTTCCTCTTC CCCCCAAAAC
     TTTCAACTCG GGTTTAGAAC ACTGTTTTGA GTGTGTACGG GTGGCACGGG TCGTGGACTT GAGGACCCCC CTGGCAGTCA GAAGGAGAAG GGGGGTTTTG
 243 K  V  E  P   K  S  C   D  K  T   H  T  C  P   P  C  P   A  P  E   L  L  G  G   P  S  V   F  L  F   P  P  K  P

2401 CCAAGGACAC CCTCATGATC TCCCGGACCC CTGAGGTCAC ATGCGTGGTG GTGGACGTGA GCCACGAAGA CCCTGAGGTC AAGTTCAACT GGTACGTGGA
     GGTTCCTGTG GGAGTACTAG AGGGCCTGGG GACTCCAGTG TACGCACCAC CACCTGCACT CGGTGCTTCT GGGACTCCAG TTCAAGTTGA CCATGCACCT
 277   K  D  T   L  M  I   S  R  T  P   E  V  T   C  V  V   V  D  V  S   H  E  D   P  E  V   K  F  N  W   Y  V  D

2501 CGGCGTGGAG GTGCATAATG CCAAGACAAA GCCGCGGGAG GAGCAGTACA ACAGCACGTA CCGTGTGGTC AGCGTCCTCA CCGTCCTGCA CCAGGACTGG
     GCCGCACCTC CACGTATTAC GGTTCTGTTT CGGCGCCCTC CTCGTCATGT TGTCGTGCAT GGCACACCAG TCGCAGGAGT GGCAGGACGT GGTCCTGACC
 310   G  V  E   V  H  N  A   K  T  K   P  R  E   E  Q  Y  N   S  T  Y   R  V  V   S  V  L  T   V  L  H   Q  D  W

2601 CTGAATGGCA AGGAGTACAA GTGCAAGGTC TCCAACAAAG CCCTCCCAGC CCCCATCGAG AAAACCATCT CCAAAGCCAA AGGGCAGCCC CGAGAACCAC
     GACTTACCGT TCCTCATGTT CACGTTCCAG AGGTTGTTTC GGGAGGGTCG GGGGTAGCTC TTTTGGTAGA GGTTTCGGTT TCCCGTCGGG GCTCTTGGTG
 343 L  N  G  K   E  Y  K   C  K  V   S  N  K  A   L  P  A   P  I  E   K  T  I  S   K  A  K   G  Q  P   R  E  P  Q

2701 AGGTGTACAC CCTGCCCCCA TCCCGGGAAG AGATGACCAA GAACCAGGTC AGCCTGACCT GCCTGGTCAA AGGCTTCTAT CCCAGCGACA TCGCCGTGGA
     TCCACATGTG GGACGGGGGT AGGGCCCTTC TCTACTGGTT CTTGGTCCAG TCGGACTGGA CGGACCAGTT TCCGAAGATA GGGTCGCTGT AGCGGCACCT
 377   V  Y  T   L  P  P   S  R  E  E   M  T  K   N  Q  V   S  L  T  C   L  V  K   G  F  Y   P  S  D  I   A  V  E

2801 GTGGGAGAGC AATGGGCAGC CGGAGAACAA CTACAAGACC ACGCCTCCCG TGCTGGACTC CGACGGCTCC TTCTTCCTCT ACAGCAAGCT CACCGTGGAC
     CACCCTCTCG TTACCCGTCG GCCTCTTGTT GATGTTCTGG TGCGGAGGGC ACGACCTGAG GCTGCCGAGG AAGAAGGAGA TGTCGTTCGA GTGGCACCTG
 410   W  E  S   N  G  Q  P   E  N  N   Y  K  T   T  P  P  V   L  D  S   D  G  S   F  F  L  Y   S  K  L   T  V  D

2901 AAGAGCAGGT GGCAGCAGGG GAACGTCTTC TCATGCTCCG TGATGCATGA GGCTCTGCAC AACCACTACA CGCAGAAGAG CCTCTCCCTG TCTCCGGGTA
     TTCTCGTCCA CCGTCGTCCC CTTGCAGAAG AGTACGAGGC ACTACGTACT CCGAGACGTG TTGGTGATGT GCGTCTTCTC GGAGAGGGAC AGAGGCCCAT
 443 K  S  R  W   Q  Q  G   N  V  F   S  C  S  V   M  H  E   A  L  H   N  H  Y  T   Q  K  S   L  S  L   S  P  G  K

3001 AATAAGCATG CGACGGCCCT AGAGTCCCTA ACGCTCGGTT GCCGCCGGGC GTTTTTTATT GTTAACTCAT GTTTGACAGC TTATCATCGA TAAGCTTTAA
     TTATTCGTAC GCTGCCGGGA TCTCAGGGAT TGCGAGCCAA CGGCGGCCCG CAAAAAATAA CAATTGAGTA CAAACTGTCG AATAGTAGCT ATTCGAAATT
 477   O

3101 TGCGGTAGTT TATCACAGTT AAATTGCTAA CGCAGTCAGG CACCGTGTAT GAAATCTAAC AATGCGCTCA TCGTCATCCT CGGCACCGTC ACCCTGGATG
     ACGCCATCAA ATAGTGTCAA TTTAACGATT GCGTCAGTCC GTGGCACATA CTTTAGATTG TTACGCGAGT AGCAGTAGGA GCCGTGGCAG TGGGACCTAC
                                                                                ^Start Tet Resistance Coding Sequence
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FIG. 19D

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3201 CTGTAGGCAT AGGCTTGGTT ATGCCGGTAC TGCCGGGCCT CTTGCGGGAT ATCGTCCATT CCGACAGCAT CGCCAGTCAC TATGGCGTGC TGCTAGCGCT
     GACATCCGTA TCCGAACCAA TACGGCCATG ACGGCCCGGA GAACGCCCTA TAGCAGGTAA GGCTGTCGTA GCGGTCAGTG ATACCGCACG ACGATCGCGA

3301
```

FIG. 20A

Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
Serial No.: 10/764,428
Sheet 35 of 50

FIG. 20B

```
1001 GCAGGACAGC AAGGACAGCA CCTACAGCCT CAGCAGCACC CTGACGCTGA GCAAAGCAGA CTACGAGAAA CACAAAGTCT ACGCCTGCGA AGTCACCCAT
     CGTCCTGTCG TTCCTGTCGT GGATGTCGGA GTCGTCGTGG GACTGCGACT CGTTTCGTCT GATGCTCTTT GTGTTTCAGA TGCGGACGCT TCAGTGGGTA
 193  Q  D  S   K  D  S  T   Y  S  L   S  S  T   L  T  L  S   K  A  D   Y  E  K   H  K  V  Y   A  C  E   V  T  H

1101 CAGGGCCTGA GCTCGCCCGT CACAAAGAGC TTCAACAGGG GAGAGTGTTA ATTAAATCCT CTACGCCGGA CGCATCGTGG CGAGCTCGGT ACCCGGGGAT
     GTCCCGGACT CGAGCGGGCA GTGTTTCTCG AAGTTGTCCC CTCTCACAAT TAATTTAGGA GATGCGGCCT GCGTAGCACC GCTCGAGCCA TGGGCCCCTA
 226 Q  G  L  S   S  P  V   T  K  S   F  N  R  G   E  C  O

1201 CTAGGCCTAA CGCTCGGTTG CCGCCGGGCG TTTTTTATTG TTGCCGACGC GCATCTCGAA TGAACTGTGT GCGCAGGTAG AAGCTTTGGA GATTATCGTC
     GATCCGGATT GCGAGCCAAC GGCGGCCCGC AAAAAATAAC AACGGCTGCG CGTAGAGCTT ACTTGACACA CGCGTCCATC TTCGAAACCT CTAATAGCAG

1301 ACTGCAATGC TTCGCAATAT GGCGCAAAAT GACCAACAGC GGTTGATTGA TCAGGTAGAG GGGGCGCTGT ACGAGGTAAA GCCCGATGCC AGCATTCCTG
     TGACGTTACG AAGCGTTATA CCGCGTTTTA CTGGTTGTCG CCAACTAACT AGTCCATCTC CCCCGCGACA TGCTCCATTT CGGGCTACGG TCGTAAGGAC

1401 ACGACGATAC GGAGCTGCTG CGCGATTACG TAAAGAAGTT ATTGAAGCAT CCTCGTCAGT AAAAAGTTAA TCTTTTCAAC AGCTGTCATA AAGTTGTCAC
     TGCTGCTATG CCTCGACGAC GCGCTAATGC ATTTCTTCAA TAACTTCGTA GGAGCAGTCA TTTTTCAATT AGAAAAGTTG TCGACAGTAT TTCAACAGTG

1501 GGCCGAGACT TATAGTCGCT TTGTTTTTAT TTTTTAATGT ATTTGTAACT AGTACGCAAG TTCACGTAAA AAGGGTATCT AGAATTATGA AGAAGAATAT
     CCGGCTCTGA ATATCAGCGA AACAAAAATA AAAAATTACA TAAACATTGA TCATGCGTTC AAGTGCATTT TTCCCATAGA TCTTAATACT TCTTCTTATA
   1                                                                                                  M  K   K  N  I
                                                                                                      ^STII Signal TIR-1

1601 CGCATTTCTT CTTGCATCTA TGTTCGTTTT TTCTATTGCT ACAAACGCGT ACGCTGAGGT TCAGCTGGTG GAGTCTGGCG GTGGCCTGGT GCAGCCAGGG
     GCGTAAAGAA GAACGTAGAT ACAAGCAAAA AAGATAACGA TGTTTGCGCA TGCGACTCCA AGTCGACCAC CTCAGACCGC CACCGGACCA CGTCGGTCCC
   6  A  F  L   L  A  S  M   F  V  F   S  I  A   T  N  A  Y   A  E  V   Q  L  V   E  S  G  G   G  L  V   Q  P  G
                                                                ^anti-IgE heavy chain

1701 GGCTCACTCC GTTTGTCCTG TGCAGTTTCT GGCTACTCCA TCACCTCCGG ATATAGCTGG AACTGGATCC GTCAGGCCCC GGGTAAGGGC CTGGAATGGG
     CCGAGTGAGG CAAACAGGAC ACGTCAAAGA CCGATGAGGT AGTGGAGGCC TATATCGACC TTGACCTAGG CAGTCCGGGG CCCATTCCCG GACCTTACCC
  39 G  S  L  R   L  S  C   A  V  S   G  Y  S  I   T  S  G   Y  S  W   N  W  I  R   Q  A  P   G  K  G   L  E  W  V

1801 TTGCATCGAT TACGTATGAC GGATCGACTA ACTATAACCC TAGCGTCAAG GGCCGTATCA CTATAAGTCG CGACGACTCC AAAAACACAT TCTACCTGCA
     AACGTAGCTA ATGCATACTG CCTAGCTGAT TGATATTGGG ATCGCAGTTC CCGGCATAGT GATATTCAGC GCTGCTGAGG TTTTTGTGTA AGATGGACGT
  73   A  S  I   T  Y  D   G  S  T  N   Y  N  P   S  V  K   G  R  I  T   I  S  R   D  D  S   K  N  T  F   Y  L  Q

1901 GATGAACAGC CTGCGTGCTG AGGACACTGC CGTCTATTAT TGTGCTCGAG GCAGCCACTA TTTCGGTCAC TGGCACTTCG CCGTGTGGGG TCAAGGAACC
     CTACTTGTCG GACGCACGAC TCCTGTGACG GCAGATAATA ACACGAGCTC CGTCGGTGAT AAAGCCAGTG ACCGTGAAGC GGCACACCCC AGTTCCTTGG
 106  M  N  S   L  R  A  E   D  T  A   V  Y  Y   C  A  R  G   S  H  Y   F  G  H   W  H  F  A   V  W  G   Q  G  T

2001 CTGGTCACCG TCTCCTCGGC CTCCACCAAG GGCCCATCGG TCTTCCCCCT GGCACCCTCC TCCAAGAGCA CCTCTGGGGG CACAGCGGCC CTGGGCTGCC
     GACCAGTGGC AGAGGAGCCG GAGGTGGTTC CCGGGTAGCC AGAAGGGGGA CCGTGGGAGG AGGTTCTCGT GGAGACCCCC GTGTCGCCGG GACCCGACGG
 139 L  V  T  V   S  S  A   S  T  K   G  P  S  V   F  P  L   A  P  S   S  K  S  T   S  G  G   T  A  A   L  G  C  L
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Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
Serial No.: 10/764,428
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FIG. 20C

```
2101 TGGTCAAGGA CTACTTCCCC GAACCGGTGA CGGTGTCGTG GAACTCAGGC GCCCTGACCA GCGGCGTGCA CACCTTCCCG GCTGTCCTAC AGTCCTCAGG
     ACCAGTTCCT GATGAAGGGG CTTGGCCACT GCCACAGCAC CTTGAGTCCG CGGGACTGGT CGCCGCACGT GTGGAAGGGC CGACAGGATG TCAGGAGTCC
 173   V  K  D   Y  F  P   E  P  V  T   V  S  W   N  S  G   A  L  T  S   G  V  H   T  F  P   A  V  L  Q   S  S  G

2201 ACTCTACTCC CTCAGCAGCG TGGTGACTGT GCCCTCTAGC AGCTTGGGCA CCCAGACCTA CATCTGCAAC GTGAATCACA AGCCCAGCAA CACCAAGGTG
     TGAGATGAGG GAGTCGTCGC ACCACTGACA CGGGAGATCG TCGAACCCGT GGGTCTGGAT GTAGACGTTG CACTTAGTGT TCGGGTCGTT GTGGTTCCAC
 206  L  Y  S   L  S  S  V   V  T  V   P  S  S   S  L  G  T   Q  T  Y   I  C  N   V  N  H  K   P  S  N   T  K  V

2301 GACAAGAAAG TTGAGCCCAA ATCTTGTGAC AAAACTCACA CATGCCCACC GTGCCCAGCA CCTGAACTCC TGGGGGGACC GTCAGTCTTC CTCTTCCCCC
     CTGTTCTTTC AACTCGGGTT TAGAACACTG TTTTGAGTGT GTACGGGTGG CACGGGTCGT GGACTTGAGG ACCCCCCTGG CAGTCAGAAG GAGAAGGGGG
 239 D  K  K  V   E  P  K   S  C  D   K  T  H  T   C  P  P   C  P  A   P  E  L  L   G  G  P   S  V  F   L  F  P  P

2401 CAAAACCCAA GGACACCCTC ATGATCTCCC GGACCCCTGA GGTCACATGC GTGGTGGTGG ACGTGAGCCA CGAAGACCCT GAGGTCAAGT TCAACTGGTA
     GTTTTGGGTT CCTGTGGGAG TACTAGAGGG CCTGGGGACT CCAGTGTACG CACCACCACC TGCACTCGGT GCTTCTGGGA CTCCAGTTCA AGTTGACCAT
 273   K  P  K   D  T  L   M  I  S  R   T  P  E   V  T  C   V  V  V  D   V  S  H   E  D  P   E  V  K  F   N  W  Y

2501 CGTGGACGGC GTGGAGGTGC ATAATGCCAA GACAAAGCCG CGGGAGGAGC AGTACAACAG CACGTACCGT GTGGTCAGCG TCCTCACCGT CCTGCACCAG
     GCACCTGCCG CACCTCCACG TATTACGGTT CTGTTTCGGC GCCCTCCTCG TCATGTTGTC GTGCATGGCA CACCAGTCGC AGGAGTGGCA GGACGTGGTC
 306  V  D  G   V  E  V  H   N  A  K   T  K  P   R  E  E  Q   Y  N  S   T  Y  R   V  V  S  V   L  T  V   L  H  Q

2601 GACTGGCTGA ATGGCAAGGA GTACAAGTGC AAGGTCTCCA ACAAAGCCCT CCCAGCCCCC ATCGAGAAAA CCATCTCCAA AGCCAAAGGG CAGCCCCGAG
     CTGACCGACT TACCGTTCCT CATGTTCACG TTCCAGAGGT TGTTTCGGGA GGGTCGGGGG TAGCTCTTTT GGTAGAGGTT TCGGTTTCCC GTCGGGGCTC
 339 D  W  L  N   G  K  E   Y  K  C   K  V  S  N   K  A  L   P  A  P   I  E  K  T   I  S  K   A  K  G   Q  P  R  E

2701 AACCACAGGT GTACACCCTG CCCCCATCCC GGGAAGAGAT GACCAAGAAC CAGGTCAGCC TGACCTGCCT GGTCAAAGGC TTCTATCCCA GCGACATCGC
     TTGGTGTCCA CATGTGGGAC GGGGGTAGGG CCCTTCTCTA CTGGTTCTTG GTCCAGTCGG ACTGGACGGA CCAGTTTCCG AAGATAGGGT CGCTGTAGCG
 373   P  Q  V   Y  T  L   P  P  S  R   E  E  M   T  K  N   Q  V  S  L   T  C  L   V  K  G   F  Y  P  S   D  I  A

2801 CGTGGAGTGG GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC GGCTCCTTCT TCCTCTACAG CAAGCTCACC
     GCACCTCACC CTCTCGTTAC CCGTCGGCCT CTTGTTGATG TTCTGGTGCG GAGGGCACGA CCTGAGGCTG CCGAGGAAGA AGGAGATGTC GTTCGAGTGG
 406  V  E  W   E  S  N  G   Q  P  E   N  N  Y   K  T  T  P   P  V  L   D  S  D   G  S  F  F   L  Y  S   K  L  T

2901 GTGGACAAGA GCAGGTGGCA GCAGGGGAAC GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC TCCCTGTCTC
     CACCTGTTCT CGTCCACCGT CGTCCCCTTG CAGAAGAGTA CGAGGCACTA CGTACTCCGA GACGTGTTGG TGATGTGCGT CTTCTCGGAG AGGGACAGAG
 439 V  D  K  S   R  W  Q   Q  G  N   V  F  S  C   S  V  M   H  E  A   L  H  N  H   Y  T  Q   K  S  L   S  L  S  P

3001 CGGGTAAATA AGCATGCGAC GGCCCTAGAG TCCCTAACGC TCGGTTGCCG CCGGGCGTTT TTTATTGTTA ACTCATGTTT GACAGCTTAT CATCGATAAG
     GCCCATTTAT TCGTACGCTG CCGGGATCTC AGGGATTGCG AGCCAACGGC GGCCCGCAAA AAATAACAAT TGAGTACAAA CTGTCGAATA GTAGCTATTC
 473   G  K  O

3101 CTTTAATGCG GTAGTTTATC ACAGTTAAAT TGCTAACGCA GTCAGGCACC GTGTATGAAA TCTAACAATG CGCTCATCGT CATCCTCGGC ACCGTCACCC
     GAAATTACGC CATCAAATAG TGTCAATTTA ACGATTGCGT CAGTCCGTGG CACATACTTT AGATTGTTAC GCGAGTAGCA GTAGGAGCCG TGGCAGTGGG
```

FIG. 20D

```
3201 TGGATGCTGT AGGCATAGGC TTGGTTATGC CGGTACTGCC GGGCCTCTTG CGGGATATCG TCCATTCCGA CAGCATCGCC AGTCACTATG GCGTGCTGCT
     ACCTACGACA TCCGTATCCG AACCAATACG GCCATGACGG CCCGGAGAAC GCCCTATAGC AGGTAAGGCT GTCGTAGCGG TCAGTGATAC CGCACGACGA


3301
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Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
Serial No.: 10/764,428
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FIG. 21A

Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
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Sheet 39 of 50

FIG. 21B

```
1001 GCAGGACAGC AAGGACAGCA CCTACAGCCT CAGCAGCACC CTGACGCTGA GCAAAGCAGA CTACGAGAAA CACAAAGTCT ACGCCTGCGA AGTCACCCAT
     CGTCCTGTCG TTCCTGTCGT GGATGTCGGA GTCGTCGTGG GACTGCGACT CGTTTCGTCT GATGCTCTTT GTGTTTCAGA TGCGGACGCT TCAGTGGGTA
 193  Q  D  S   K  D  S  T   Y  S  L   S  S  T   L  T  L  S   K  A  D   Y  E  K   H  K  V  Y   A  C  E   V  T  H

1101 CAGGGCCTGA GCTCGCCCGT CACAAAGAGC TTCAACAGGG GAGAGTGTTA ATTAAATCCT CTACGCCGGA CGCATCGTGG CGAGCTCGGT ACCCGGGGAT
     GTCCCGGACT CGAGCGGGCA GTGTTTCTCG AAGTTGTCCC CTCTCACAAT TAATTTAGGA GATGCGGCCT GCGTAGCACC GCTCGAGCCA TGGGCCCCTA
 226 Q  G  L  S   S  P  V   T  K  S   F  N  R  G   E  C  O

1201 CTAGGCCTAA CGCTCGGTTG CCGCCGGGCG TTTTTTATTG TTGCCGACGC GCATCTCGAA TGAACTGTGT GCGCAGGTAG AAGCTTTGGA GATTATCGTC
     GATCCGGATT GCGAGCCAAC GGCGGCCCGC AAAAAATAAC AACGGCTGCG CGTAGAGCTT ACTTGACACA CGCGTCCATC TTCGAAACCT CTAATAGCAG

1301 ACTGCAATGC TTCGCAATAT GGCGCAAAAT GACCAACAGC GGTTGATTGA TCAGGTAGAG GGGGCGCTGT ACGAGGTAAA GCCCGATGCC AGCATTCCTG
     TGACGTTACG AAGCGTTATA CCGCGTTTTA CTGGTTGTCG CCAACTAACT AGTCCATCTC CCCCGCGACA TGCTCCATTT CGGGCTACGG TCGTAAGGAC

1401 ACGACGATAC GGAGCTGCTG CGCGATTACG TAAAGAAGTT ATTGAAGCAT CCTCGTCAGT AAAAAGTTAA TCTTTTCAAC AGCTGTCATA AAGTTGTCAC
     TGCTGCTATG CCTCGACGAC GCGCTAATGC ATTTCTTCAA TAACTTCGTA GGAGCAGTCA TTTTTCAATT AGAAAAGTTG TCGACAGTAT TTCAACAGTG

1501 GGCCGAGACT TATAGTCGCT TTGTTTTTAT TTTTTAATGT ATTTGTAACT AGTACGCAAG TTCACGTAAA AAGGGTATCT AGAATTATGA AGAAGAATAT
     CCGGCTCTGA ATATCAGCGA AACAAAAATA AAAAATTACA TAAACATTGA TCATGCGTTC AAGTGCATTT TTCCCATAGA TCTTAATACT TCTTCTTATA
   1                                                                                                  M  K   K  N  I
                                                                                                      ^STII Signal TIR-1

1601 CGCATTTCTT CTTGCATCTA TGTTCGTTTT TTCTATTGCT ACAAACGCGT ACGCTCAGGT TCAGCTGCAA GAGTCTGGCC CGGGCCTGGT GAAACCATCT
     GCGTAAAGAA GAACGTAGAT ACAAGCAAAA AAGATAACGA TGTTTGCGCA TGCGAGTCCA AGTCGACGTT CTCAGACCGG GCCCGGACCA CTTTGGTAGA
   6  A  F  L   L  A  S  M   F  V  F   S  I  A   T  N  A  Y   A  Q  V   Q  L  Q   E  S  G  P   G  L  V   K  P  S
                                                                ^anti-IgE Heavy Chain
                                                                ^Heavy Chain FR1=SubgroupII consensus sequence

1701 CAGACTCTCT CCTTGACTTG TACTGTTTCT GGCTACTCCA TCACCTCCGG ATATAGCTGG AACTGGATCC GTCAGGCCCC GGGTAAGGGC CTGGAATGGG
     GTCTGAGAGA GGAACTGAAC ATGACAAAGA CCGATGAGGT AGTGGAGGCC TATATCGACC TTGACCTAGG CAGTCCGGGG CCCATTCCCG GACCTTACCC
  39 Q  T  L  S   L  T  C   T  V  S   G  Y  S  I   T  S  G   Y  S  W   N  W  I  R   Q  A  P   G  K  G   L  E  W  V

1801 TTGCATCGAT TACGTATGAC GGATCGACTA ACTATAACCC TAGCGTCAAG GGCCGTATCA CTATAAGTCG CGACGACTCC AAAAACACAT TCTACCTGCA
     AACGTAGCTA ATGCATACTG CCTAGCTGAT TGATATTGGG ATCGCAGTTC CCGGCATAGT GATATTCAGC GCTGCTGAGG TTTTTGTGTA AGATGGACGT
  73   A  S  I   T  Y  D   G  S  T  N   Y  N  P   S  V  K   G  R  I  T   I  S  R   D  D  S   K  N  T  F   Y  L  Q

1901 GATGAACAGC CTGCGTGCTG AGGACACTGC CGTCTATTAT TGTGCTCGAG GCAGCCACTA TTTCGGTCAC TGGCACTTCG CCGTGTGGGG TCAAGGAACC
     CTACTTGTCG GACGCACGAC TCCTGTGACG GCAGATAATA ACACGAGCTC CGTCGGTGAT AAAGCCAGTG ACCGTGAAGC GGCACACCCC AGTTCCTTGG
 106  M  N  S   L  R  A  E   D  T  A   V  Y  Y   C  A  R  G   S  H  Y   F  G  H   W  H  F  A   V  W  G   Q  G  T

2001 CTGGTCACCG TCTCCTCGGC CTCCACCAAG GGCCCATCGG TCTTCCCCCT GGCACCCTCC TCCAAGAGCA CCTCTGGGGG CACAGCGGCC CTGGGCTGCC
     GACCAGTGGC AGAGGAGCCG GAGGTGGTTC CCGGGTAGCC AGAAGGGGGA CCGTGGGAGG AGGTTCTCGT GGAGACCCCC GTGTCGCCGG GACCCGACGG
 139 L  V  T  V   S  S  A   S  T  K   G  P  S  V   F  P  L   A  P  S   S  K  S  T   S  G  G   T  A  A   L  G  C  L
```

Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
Serial No.: 10/764,428
Sheet 40 of 50

FIG. 21C

```
2101 TGGTCAAGGA CTACTTCCCC GAACCGGTGA CGGTGTCGTG GAACTCAGGC GCCCTGACCA GCGGCGTGCA CACCTTCCCG GCTGTCCTAC AGTCCTCAGG
     ACCAGTTCCT GATGAAGGGG CTTGGCCACT GCCACAGCAC CTTGAGTCCG CGGGACTGGT CGCCGCACGT GTGGAAGGGC CGACAGGATG TCAGGAGTCC
 173   V  K  D   Y  F  P   E  P  V  T   V  S  W   N  S  G   A  L  T  S   G  V  H   T  F  P   A  V  L  Q   S  S  G

2201 ACTCTACTCC CTCAGCAGCG TGGTGACTGT GCCCTCTAGC AGCTTGGGCA CCCAGACCTA CATCTGCAAC GTGAATCACA AGCCCAGCAA CACCAAGGTG
     TGAGATGAGG GAGTCGTCGC ACCACTGACA CGGGAGATCG TCGAACCCGT GGGTCTGGAT GTAGACGTTG CACTTAGTGT TCGGGTCGTT GTGGTTCCAC
 206  L  Y  S   L  S  S  V   V  T  V   P  S  S   S  L  G  T   Q  T  Y   I  C  N   V  N  H  K   P  S  N   T  K  V

2301 GACAAGAAAG TTGAGCCCAA ATCTTGTGAC AAAACTCACA CATGCCCACC GTGCCCAGCA CCTGAACTCC TGGGGGGACC GTCAGTCTTC CTCTTCCCCC
     CTGTTCTTTC AACTCGGGTT TAGAACACTG TTTTGAGTGT GTACGGGTGG CACGGGTCGT GGACTTGAGG ACCCCCCTGG CAGTCAGAAG GAGAAGGGGG
 239 D  K  K  V   E  P  K   S  C  D   K  T  H  T   C  P  P   C  P  A   P  E  L  L   G  G  P   S  V  F   L  F  P  P

2401 CAAAACCCAA GGACACCCTC ATGATCTCCC GGACCCCTGA GGTCACATGC GTGGTGGTGG ACGTGAGCCA CGAAGACCCT GAGGTCAAGT TCAACTGGTA
     GTTTTGGGTT CCTGTGGGAG TACTAGAGGG CCTGGGGACT CCAGTGTACG CACCACCACC TGCACTCGGT GCTTCTGGGA CTCCAGTTCA AGTTGACCAT
 273   K  P  K   D  T  L   M  I  S  R   T  P  E   V  T  C   V  V  V  D   V  S  H   E  D  P   E  V  K  F   N  W  Y

2501 CGTGGACGGC GTGGAGGTGC ATAATGCCAA GACAAAGCCG CGGGAGGAGC AGTACAACAG CACGTACCGT GTGGTCAGCG TCCTCACCGT CCTGCACCAG
     GCACCTGCCG CACCTCCACG TATTACGGTT CTGTTTCGGC GCCCTCCTCG TCATGTTGTC GTGCATGGCA CACCAGTCGC AGGAGTGGCA GGACGTGGTC
 306  V  D  G   V  E  V  H   N  A  K   T  K  P   R  E  E  Q   Y  N  S   T  Y  R   V  V  S  V   L  T  V   L  H  Q

2601 GACTGGCTGA ATGGCAAGGA GTACAAGTGC AAGGTCTCCA ACAAAGCCCT CCCAGCCCCC ATCGAGAAAA CCATCTCCAA AGCCAAAGGG CAGCCCCGAG
     CTGACCGACT TACCGTTCCT CATGTTCACG TTCCAGAGGT TGTTTCGGGA GGGTCGGGGG TAGCTCTTTT GGTAGAGGTT TCGGTTTCCC GTCGGGGCTC
 339 D  W  L  N   G  K  E   Y  K  C   K  V  S  N   K  A  L   P  A  P   I  E  K  T   I  S  K   A  K  G   Q  P  R  E

2701 AACCACAGGT GTACACCCTG CCCCCATCCC GGGAAGAGAT GACCAAGAAC CAGGTCAGCC TGACCTGCCT GGTCAAAGGC TTCTATCCCA GCGACATCGC
     TTGGTGTCCA CATGTGGGAC GGGGGTAGGG CCCTTCTCTA CTGGTTCTTG GTCCAGTCGG ACTGGACGGA CCAGTTTCCG AAGATAGGGT CGCTGTAGCG
 373   P  Q  V   Y  T  L   P  P  S  R   E  E  M   T  K  N   Q  V  S  L   T  C  L   V  K  G   F  Y  P  S   D  I  A

2801 CGTGGAGTGG GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC GGCTCCTTCT TCCTCTACAG CAAGCTCACC
     GCACCTCACC CTCTCGTTAC CCGTCGGCCT CTTGTTGATG TTCTGGTGCG GAGGGCACGA CCTGAGGCTG CCGAGGAAGA AGGAGATGTC GTTCGAGTGG
 406  V  E  W   E  S  N  G   Q  P  E   N  N  Y   K  T  T  P   P  V  L   D  S  D   G  S  F  F   L  Y  S   K  L  T

2901 GTGGACAAGA GCAGGTGGCA GCAGGGGAAC GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC TCCCTGTCTC
     CACCTGTTCT CGTCCACCGT CGTCCCCTTG CAGAAGAGTA CGAGGCACTA CGTACTCCGA GACGTGTTGG TGATGTGCGT CTTCTCGGAG AGGGACAGAG
 439 V  D  K  S   R  W  Q   Q  G  N   V  F  S  C   S  V  M   H  E  A   L  H  N  H   Y  T  Q   K  S  L   S  L  S  P

3001 CGGGTAAATA AGCATGCGAC GGCCCTAGAG TCCCTAACGC TCGGTTGCCG CCGGGCGTTT TTTATTGTTA ACTCATGTTT GACAGCTTAT CATCGATAAG
     GCCCATTTAT TCGTACGCTG CCGGGATCTC AGGGATTGCG AGCCAACGGC GGCCCGCAAA AAATAACAAT TGAGTACAAA CTGTCGAATA GTAGCTATTC
 473   G  K  O

3101 CTTTAATGCG GTAGTTTATC ACAGTTAAAT TGCTAACGCA GTCAGGCACC GTGTATGAAA TCTAACAATG CGCTCATCGT CATCCTCGGC ACCGTCACCC
     GAAATTACGC CATCAAATAG TGTCAATTTA ACGATTGCGT CAGTCCGTGG CACATACTTT AGATTGTTAC GCGAGTAGCA GTAGGAGCCG TGGCAGTGGG
```

FIG. 21D

```
3201 TGGATGCTGT AGGCATAGGC TTGGTTATGC CGGTACTGCC GGGCCTCTTG CGGGATATCG TCCATTCCGA CAGCATCGCC AGTCACTATG GCGTGCTGCT
     ACCTACGACA TCCGTATCCG AACCAATACG GCCATGACGG CCCGGAGAAC GCCCTATAGC AGGTAAGGCT GTCGTAGCGG TCAGTGATAC CGCACGACGA

3301
```

FIG. 22A

Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
Serial No.: 10/764,428
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FIG. 22B

```
1001 GGACAGCACC TACAGCCTCA GCAGCACCCT GACGCTGAGC AAAGCAGACT ACGAGAAACA CAAAGTCTAC GCCTGCGAAG TCACCCATCA GGGCCTGAGC
     CCTGTCGTGG ATGTCGGAGT CGTCGTGGGA CTGCGACTCG TTTCGTCTGA TGCTCTTTGT GTTTCAGATG CGGACGCTTC AGTGGGTAGT CCCGGACTCG
 193  D  S  T   Y  S  L  S   S  T  L   T  L  S   K  A  D  Y   E  K  H   K  V  Y   A  C  E  V   T  H  Q   G  L  S

1101 TCGCCCGTCA CAAAGAGCTT CAACAGGGGA GAGTGTTAAT TAAATCCTCT ACGCCGGACG CATCGTGGCG AGCTCGGTAC CCGGGGATCT AGGCCTAACG
     AGCGGGCAGT GTTTCTCGAA GTTGTCCCCT CTCACAATTA ATTTAGGAGA TGCGGCCTGC GTAGCACCGC TCGAGCCATG GGCCCCTAGA TCCGGATTGC
 226 S  P  V  T   K  S  F   N  R  G   E  C  O

1201 CTCGGTTGCC GCCGGGCGTT TTTTATTGTT GCCGACGCGC ATCTCGAATG AACTGTGTGC GCAGGTAGAA GCTTTGGAGA TTATCGTCAC TGCAATGCTT
     GAGCCAACGG CGGCCCGCAA AAAATAACAA CGGCTGCGCG TAGAGCTTAC TTGACACACG CGTCCATCTT CGAAACCTCT AATAGCAGTG ACGTTACGAA

1301 CGCAATATGG CGCAAAATGA CCAACAGCGG TTGATTGATC AGGTAGAGGG GGCGCTGTAC GAGGTAAAGC CCGATGCCAG CATTCCTGAC GACGATACGG
     GCGTTATACC GCGTTTTACT GGTTGTCGCC AACTAACTAG TCCATCTCCC CCGCGACATG CTCCATTTCG GGCTACGGTC GTAAGGACTG CTGCTATGCC

1401 AGCTGCTGCG CGATTACGTA AAGAAGTTAT TGAAGCATCC TCGTCAGTAA AAAGTTAATC TTTTCAACAG CTGTCATAAA GTTGTCACGG CCGAGACTTA
     TCGACGACGC GCTAATGCAT TTCTTCAATA ACTTCGTAGG AGCAGTCATT TTTCAATTAG AAAAGTTGTC GACAGTATTT CAACAGTGCC GGCTCTGAAT

1501 TAGTCGCTTT GTTTTTATTT TTTAATGTAT TTGTAACTAG TACGCAAGTT CACGTAAAAA GGGTATCTAG AATTATGAAG AAGAATATCG CATTTCTTCT
     ATCAGCGAAA CAAAAATAAA AAATTACATA AACATTGATC ATGCGTTCAA GTGCATTTTT CCCATAGATC TTAATACTTC TTCTTATAGC GTAAAGAAGA
   1                                                                                    M  K   K  N  I  A   F  L  L
                                                                                       ^STII Signal TIR-1

1601 TGCATCTATG TTCGTTTTTT CTATTGCTAC AAACGCGTAC GCTGAGGTTC AGCTGGTGGA GTCTGGCGGT GGCCTGGTGC AGCCAGGGGG CTCACTCCGT
     ACGTAGATAC AAGCAAAAAA GATAACGATG TTTGCGCATG CGACTCCAAG TCGACCACCT CAGACCGCCA CCGGACCACG TCGGTCCCCC GAGTGAGGCA
  10  A  S  M   F  V  F  S   I  A  T   N  A  Y   A  E  V  Q   L  V  E   S  G  G   G  L  V  Q   P  G  G   S  L  R
                                                 ^anti-VEGF (1st generation) heavy chain

1701 TTGTCCTGTG CAGCTTCTGG CTATACCTTC ACCAACTATG GTATGAACTG GGTCCGTCAG GCCCCGGGTA AGGGCCTGGA ATGGGTTGGA TGGATTAACA
     AACAGGACAC GTCGAAGACC GATATGGAAG TGGTTGATAC CATACTTGAC CCAGGCAGTC CGGGGCCCAT TCCCGGACCT TACCCAACCT ACCTAATTGT
  43 L  S  C  A   A  S  G   Y  T  F   T  N  Y  G   M  N  W   V  R  Q   A  P  G  K   G  L  E   W  V  G   W  I  N  T

1801 CCTATACCGG TGAACCGACC TATGCTGCGG ATTTCAAACG TCGTTTCACT TTCAGCTTAG ACACCTCCAA GTCGACAGCA TACCTGCAGA TGAACAGCCT
     GGATATGGCC ACTTGGCTGG ATACGACGCC TAAAGTTTGC AGCAAAGTGA AAGTCGAATC TGTGGAGGTT CAGCTGTCGT ATGGACGTCT ACTTGTCGGA
  77   Y  T  G   E  P  T   Y  A  A  D   F  K  R   R  F  T   F  S  L  D   T  S  K   S  T  A   Y  L  Q  M   N  S  L

1901 GCGTGCTGAG GACACTGCCG TCTATTACTG TGCAAAGTAC CCCCACTATT ATGGGAGCAG CCACTGGTAT TTCGACGTCT GGGGTCAAGG AACCCTGGTC
     CGCACGACTC CTGTGACGGC AGATAATGAC ACGTTTCATG GGGGTGATAA TACCCTCGTC GGTGACCATA AAGCTGCAGA CCCCAGTTCC TTGGGACCAG
 110  R  A  E   D  T  A  V   Y  Y  C   A  K  Y   P  H  Y  Y   G  S  S   H  W  Y   F  D  V  W   G  Q  G   T  L  V

2001 ACCGTCTCCT CGGCCTCCAC CAAGGGCCCA TCGGTCTTCC CCCTGGCACC CTCCTCCAAG AGCACCTCTG GGGGCACAGC GGCCCTGGGC TGCCTGGTCA
     TGGCAGAGGA GCCGGAGGTG GTTCCCGGGT AGCCAGAAGG GGGACCGTGG GAGGAGGTTC TCGTGGAGAC CCCCGTGTCG CCGGGACCCG ACGGACCAGT
 143 T  V  S  S   A  S  T   K  G  P   S  V  F  P   L  A  P   S  S  K   S  T  S  G   G  T  A   A  L  G   C  L  V  K
```

Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
Serial No.: 10/764,428
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FIG. 22C

```
2101 AGGACTACTT CCCCGAACCG GTGACGGTGT CGTGGAACTC AGGCGCCCTG ACCAGCGGCG TGCACACCTT CCCGGCTGTC CTACAGTCCT CAGGACTCTA
     TCCTGATGAA GGGGCTTGGC CACTGCCACA GCACCTTGAG TCCGCGGGAC TGGTCGCCGC ACGTGTGGAA GGGCCGACAG GATGTCAGGA GTCCTGAGAT
 177   D  Y  F   P  E  P   V  T  V  S   W  N  S   G  A  L   T  S  G  V   H  T  F   P  A  V   L  Q  S  S   G  L  Y

2201 CTCCCTCAGC AGCGTGGTGA CTGTGCCCTC TAGCAGCTTG GGCACCCAGA CCTACATCTG CAACGTGAAT CACAAGCCCA GCAACACCAA GGTGGACAAG
     GAGGGAGTCG TCGCACCACT GACACGGGAG ATCGTCGAAC CCGTGGGTCT GGATGTAGAC GTTGCACTTA GTGTTCGGGT CGTTGTGGTT CCACCTGTTC
 210   S  L  S   S  V  V   T  V  P  S   S  S  L   G  T  Q   T  Y  I  C   N  V  N   H  K  P  S   N  T  K   V  D  K

2301 AAAGTTGAGC CCAAATCTTG TGACAAAACT CACACATGCC CACCGTGCCC AGCACCTGAA CTCCTGGGGG GACCGTCAGT CTTCCTCTTC CCCCCAAAAC
     TTTCAACTCG GGTTTAGAAC ACTGTTTTGA GTGTGTACGG GTGGCACGGG TCGTGGACTT GAGGACCCCC CTGGCAGTCA GAAGGAGAAG GGGGGTTTTG
 243 K  V  E  P   K  S  C   D  K  T   H  T  C  P   P  C  P   A  P  E   L  L  G  G   P  S  V   F  L  F   P  P  K  P

2401 CCAAGGACAC CCTCATGATC TCCCGGACCC CTGAGGTCAC ATGCGTGGTG GTGGACGTGA GCCACGAAGA CCCTGAGGTC AAGTTCAACT GGTACGTGGA
     GGTTCCTGTG GGAGTACTAG AGGGCCTGGG GACTCCAGTG TACGCACCAC CACCTGCACT CGGTGCTTCT GGGACTCCAG TTCAAGTTGA CCATGCACCT
 277   K  D  T   L  M  I   S  R  T  P   E  V  T   C  V  V   V  D  V  S   H  E  D   P  E  V   K  F  N  W   Y  V  D

2501 CGGCGTGGAG GTGCATAATG CCAAGACAAA GCCGCGGGAG GAGCAGTACA ACAGCACGTA CCGTGTGGTC AGCGTCCTCA CCGTCCTGCA CCAGGACTGG
     GCCGCACCTC CACGTATTAC GGTTCTGTTT CGGCGCCCTC CTCGTCATGT TGTCGTGCAT GGCACACCAG TCGCAGGAGT GGCAGGACGT GGTCCTGACC
 310   G  V  E   V  H  N  A   K  T  K   P  R  E   E  Q  Y  N   S  T  Y   R  V  V   S  V  L  T   V  L  H   Q  D  W

2601 CTGAATGGCA AGGAGTACAA GTGCAAGGTC TCCAACAAAG CCCTCCCAGC CCCCATCGAG AAAACCATCT CCAAAGCCAA AGGGCAGCCC CGAGAACCAC
     GACTTACCGT TCCTCATGTT CACGTTCCAG AGGTTGTTTC GGGAGGGTCG GGGGTAGCTC TTTTGGTAGA GGTTTCGGTT TCCCGTCGGG GCTCTTGGTG
 343 L  N  G  K   E  Y  K   C  K  V   S  N  K  A   L  P  A   P  I  E   K  T  I  S   K  A  K   G  Q  P   R  E  P  Q

2701 AGGTGTACAC CCTGCCCCCA TCCCGGGAAG AGATGACCAA GAACCAGGTC AGCCTGACCT GCCTGGTCAA AGGCTTCTAT CCCAGCGACA TCGCCGTGGA
     TCCACATGTG GGACGGGGGT AGGGCCCTTC TCTACTGGTT CTTGGTCCAG TCGGACTGGA CGGACCAGTT TCCGAAGATA GGGTCGCTGT AGCGGCACCT
 377   V  Y  T   L  P  P   S  R  E  E   M  T  K   N  Q  V   S  L  T  C   L  V  K   G  F  Y   P  S  D  I   A  V  E

2801 GTGGGAGAGC AATGGGCAGC CGGAGAACAA CTACAAGACC ACGCCTCCCG TGCTGGACTC CGACGGCTCC TTCTTCCTCT ACAGCAAGCT CACCGTGGAC
     CACCCTCTCG TTACCCGTCG GCCTCTTGTT GATGTTCTGG TGCGGAGGGC ACGACCTGAG GCTGCCGAGG AAGAAGGAGA TGTCGTTCGA GTGGCACCTG
 410   W  E  S   N  G  Q  P   E  N  N   Y  K  T   T  P  P  V   L  D  S   D  G  S   F  F  L  Y   S  K  L   T  V  D

2901 AAGAGCAGGT GGCAGCAGGG GAACGTCTTC TCATGCTCCG TGATGCATGA GGCTCTGCAC AACCACTACA CGCAGAAGAG CCTCTCCCTG TCTCCGGGTA
     TTCTCGTCCA CCGTCGTCCC CTTGCAGAAG AGTACGAGGC ACTACGTACT CCGAGACGTG TTGGTGATGT GCGTCTTCTC GGAGAGGGAC AGAGGCCCAT
 443 K  S  R  W   Q  Q  G   N  V  F   S  C  S  V   M  H  E   A  L  H   N  H  Y  T   Q  K  S   L  S  L   S  P  G  K

3001 AATAAGCATG CGACGGCCCT AGAGTCCCTA ACGCTCGGTT GCCGCCGGGC GTTTTTTATT GTTAACTCAT GTTTGACAGC TTATCATCGA TAAGCTTTAA
     TTATTCGTAC GCTGCCGGGA TCTCAGGGAT TGCGAGCCAA CGGCGGCCCG CAAAAAATAA CAATTGAGTA CAAACTGTCG AATAGTAGCT ATTCGAAATT
 477   O

3101 TGCGGTAGTT TATCACAGTT AAATTGCTAA CGCAGTCAGG CACCGTGTAT GAAATCTAAC AATGCGCTCA TCGTCATCCT CGGCACCGTC ACCCTGGATG
     ACGCCATCAA ATAGTGTCAA TTTAACGATT GCGTCAGTCC GTGGCACATA CTTTAGATTG TTACGCGAGT AGCAGTAGGA GCCGTGGCAG TGGGACCTAC

3201 CTGTAGGCAT AGGCTTGGTT ATGCCGGTAC TGCCGGGCCT CTTGCGGGAT ATCGTCCATT CCGACAGCAT CGCCAGTCAC TATGGCGTGC TGCTAGCGCT
     GACATCCGTA TCCGAACCAA TACGGCCATG ACGGCCCGGA GAACGCCCTA TAGCAGGTAA GGCTGTCGTA GCGGTCAGTG ATACCGCACG ACGATCGCGA
```

Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
Serial No.: 10/764,428
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FIG. 23A

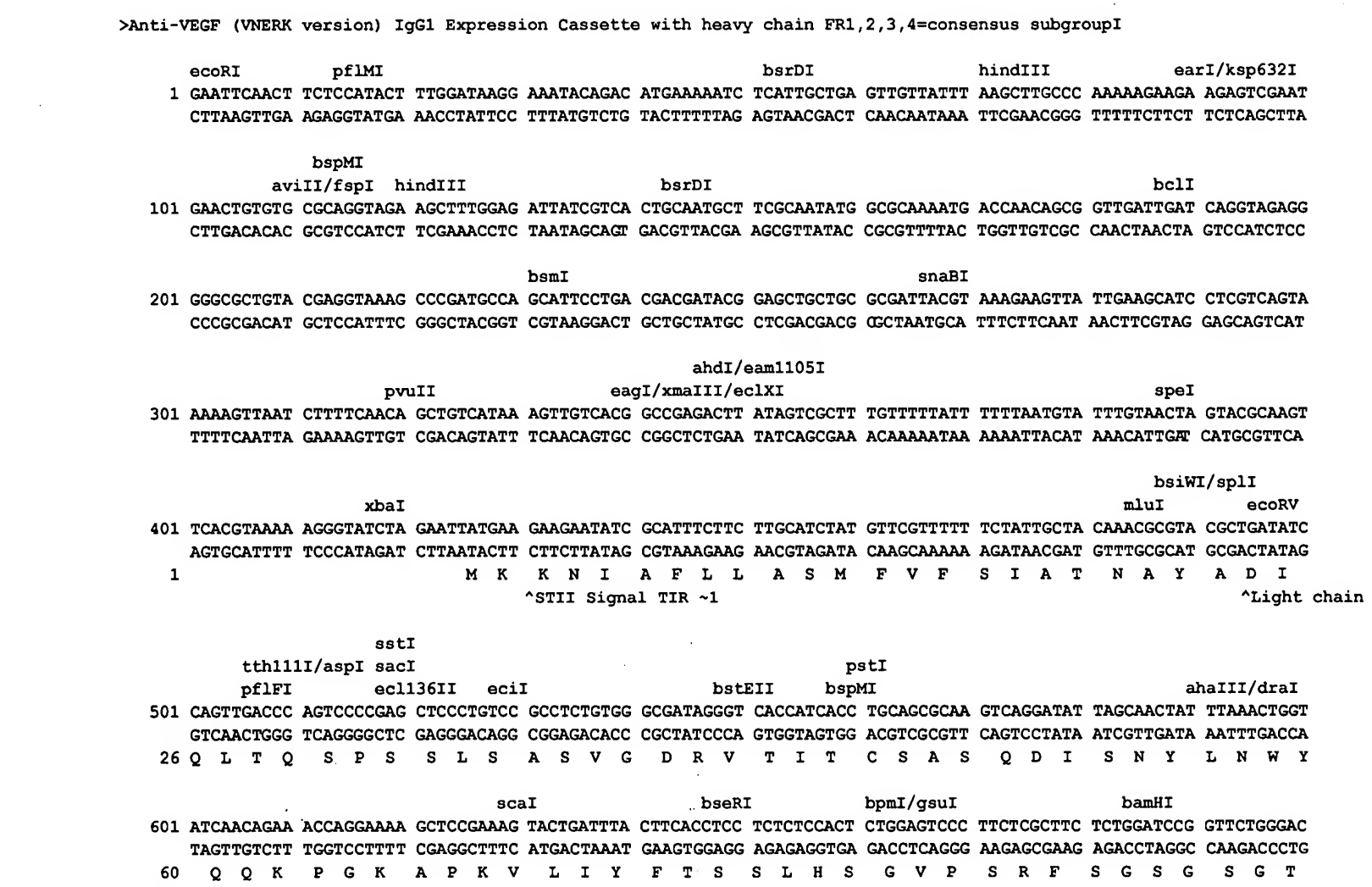
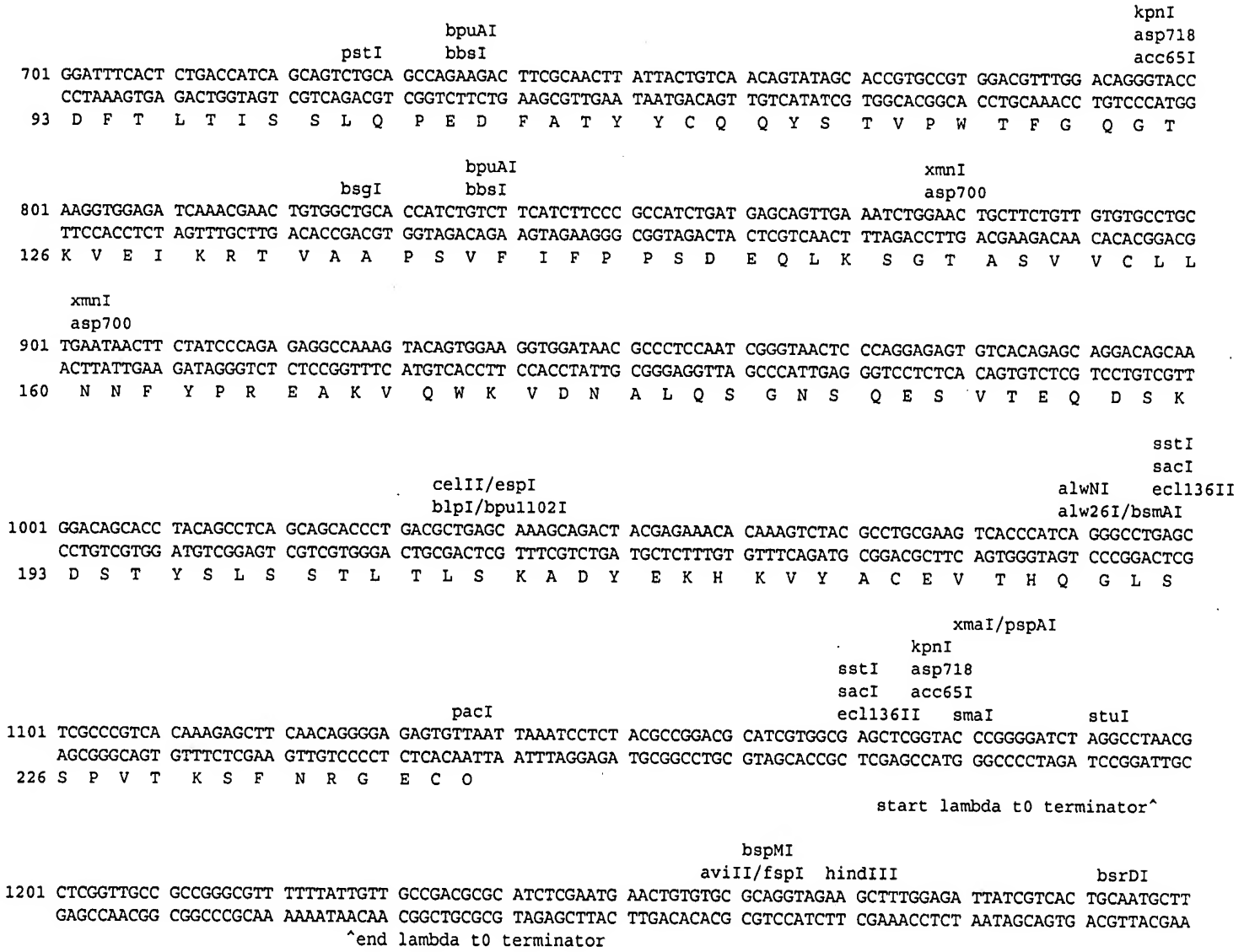

>Anti-VEGF (VNERK version) IgG1 Expression Cassette with heavy chain FR1,2,3,4=consensus subgroupI
ecoRI
pflMI
bsrDI
hindIII
earI/ksp632I
bspMI
aviII/fspI
hindIII
bsrDI
bclI
bsmI
snaBI
ahdI/eam1105I
pvuII
eagI/xmaIII/eclXI
speI
bsiWI/splI
xbaI
mluI
ecoRV
M K K N I A F L L A S M F V F S I A T N A Y A D I
^STII Signal TIR ~1
^Light chain
sstI
tth111I/aspI
sacI
pstI
pflFI
ecl136II
eciI
bstEII
bspMI
ahaIII/draI
Q L T Q S P S S L S A S V G D R V T I T C S A S Q D I S N Y L N W Y
scaI
bseRI
bpmI/gsuI
bamHI
Q Q K P G K A P K V L I Y F T S S L H S G V P S R F S G S G S G T

FIG. 23B



Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
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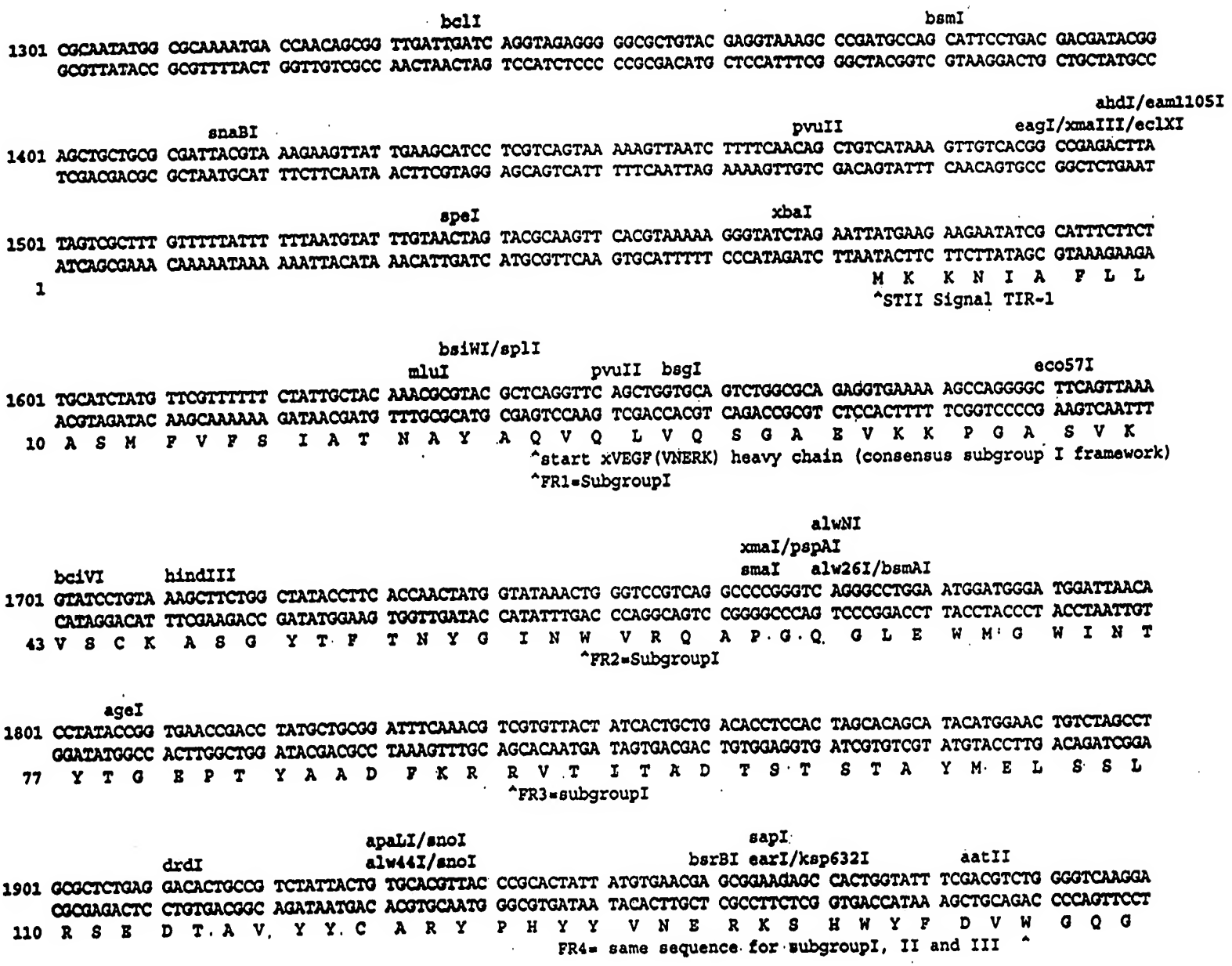

FIG.23C

Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
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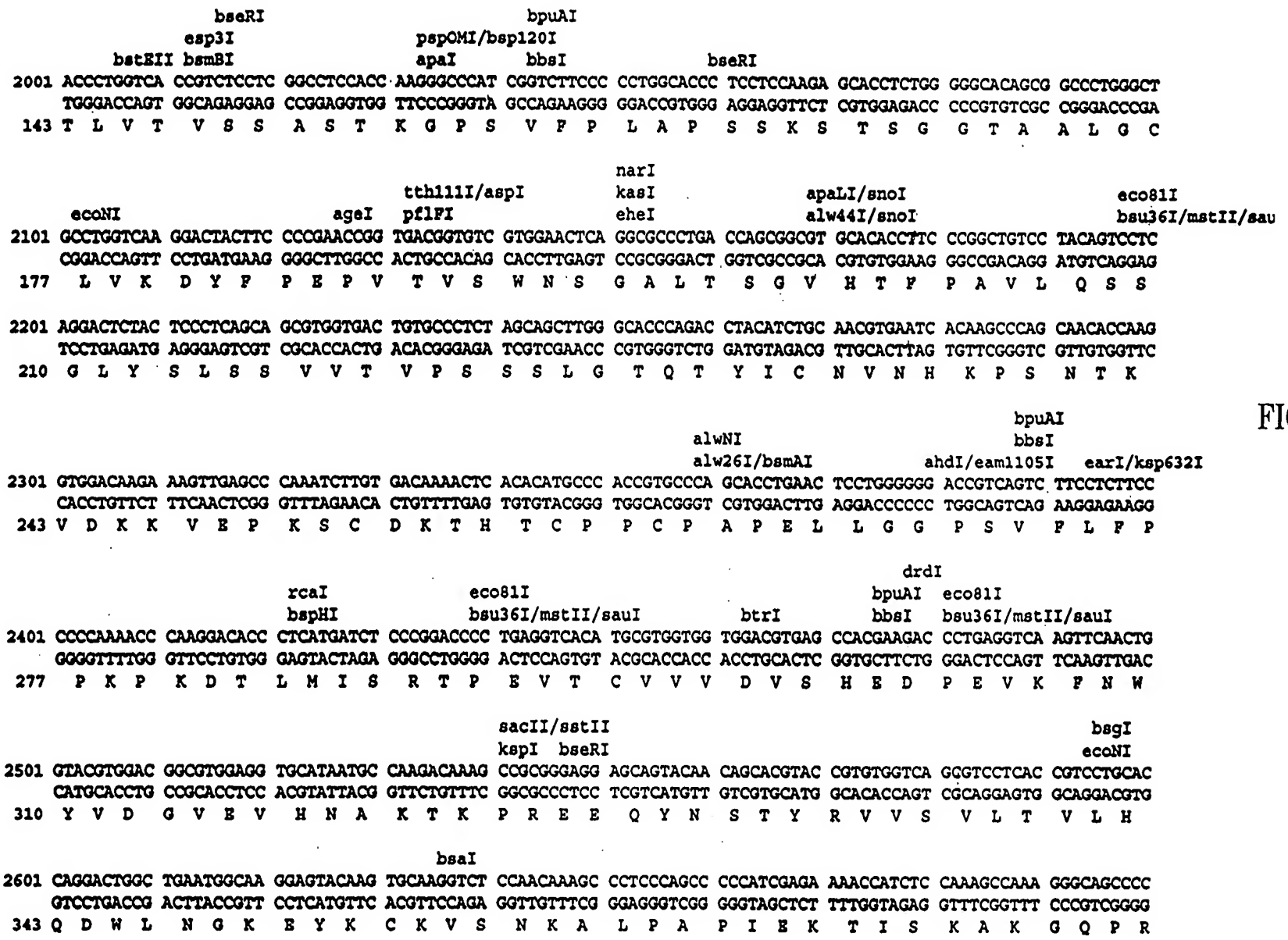

FIG.23D

Inventor: SIMMONS
Docket No.: 11669.120USU1
Title: METHODS FOR PRODUCING HUMANIZED ANTIBODIES AND IMPROVING YIELD OF ANTIBODIES OR ANTIGEN BINDING FRAGMENTS IN CELL CULTURE
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```
                                        xmaI/pspAI
                  bsp1407I/bsrGI        smaI earI/ksp632I      sexAI          bspMI
2701 GAGAACCACA GGTGTACACC CTGCCCCCAT CCCGGGAAGA GATGACCAAG AACCAGGTCA GCCTGACCTG CCTGGTCAAA GGCTTCTATC CCAGCGACAT
     CTCTTGGTGT CCACATGTGG GACGGGGGTA GGGCCCTTCT CTACTGGTTC TTGGTCCAGT CGGACTGGAC GGACCAGTTT CCGAAGATAG GGTCGCTGTA
 377   E P Q   V Y T   L P P S   R E E   M T K   N Q V S   L T C   L V K   G F Y P   S D I

                       bsrDI
2801 CGCCGTGGAG TGGGAGAGCA ATGGGCAGCC GGAGAACAAC TACAAGACCA CGCCTCCCGT GCTGGACTCC GACGGCTCCT TCTTCCTCTA CAGCAAGCTC
     GCGGCACCTC ACCCTCTCGT TACCCGTCGG CCTCTTGTTG ATGTTCTGGT GCGGAGGGCA CGACCTGAGG CTGCCGAGGA AGAAGGAGAT GTCGTTCGAG
 410 A V E   W E S N   G Q P   E N N   Y K T T   P P V   L D S   D G S F   F L Y   S K L

                                        bpuAI
                                   xmnI bbsI                ppu10I                          sapI
                  bspMI            asp700                   nsiI/avaIII  bsgI               earI/ksp632I
2901 ACCGTGGACA AGAGCAGGTG GCAGCAGGGG AACGTCTTCT CATGCTCCGT GATGCATGAG GCTCTGCACA ACCACTACAC GCAGAAGAGC CTCTCCCTGT
     TGGCACCTGT TCTCGTCCAC CGTCGTCCCC TTGCAGAAGA GTACGAGGCA CTACGTACTC CGAGACGTGT TGGTGATGTG CGTCTTCTCG GAGAGGGACA
 443 T V D K   S R W   Q Q G   N V F S   C S V   M H E   A L H N   H Y T   Q K S   L S L S

                                                                                          claI/bsp106
                     sphI                                                    hpaI         bspDI
3001 CTCCGGGTAA ATAAGCATGC GACGGCCCTA GAGTCCCTAA CGCTCGGTTG CCGCCGGGCG TTTTTTATTG TTAACTCATG TTTGACAGCT TATCATCGAT
     GAGGCCCATT TATTCGTACG CTGCCGGGAT CTCAGGGATT GCGAGCCAAC GGCGGCCCGC AAAAAATAAC AATTGAGTAC AAACTGTCGA ATAGTAGCTA
 477   P G K   O
                                                ^lambda to terminator

     hindIII
3101 AAGCTTTAAT GCGGTAGTTT ATCACAGTTA AATTGCTAAC GCAGTCAGGC ACCGTGTATG AAATCTAACA ATGCGCTCAT CGTCATCCTC GGCACCGTCA
     TTCGAAATTA CGCCATCAAA TAGTGTCAAT TTAACGATTG CGTCAGTCCG TGGCACATAC TTTAGATTGT TACGCGAGTA GCAGTAGGAG CCGTGGCAGT

                                                ecoRV
3201 CCCTGGATGC TGTAGGCATA GGCTTGGTTA TGCCGGTACT GCCGGGCCTC TTGCGGGATA TCGTCCATTC CGACAGCATC GCCAGTCACT ATGGCGTGCT
     GGGACCTACG ACATCCGTAT CCGAACCAAT ACGGCCATGA CGGCCCGGAG AACGCCCTAT AGCAGGTAAG GCTGTCGTAG CGGTCAGTGA TACCGCACGA

3301
```

> length: 3300

aatII(GACGTC): 1983
acc65I(GGTACC): 795 1176
ageI(ACCGGT): 1806 2126
ahaIII(TTTAAA): 590
ahdI(GACNNNNNGTC): 346 1495 2380
alw26I(CAGNNNCTG): 1089 1770 2359
alw44I(GTGCAC): 1930 2169

FIG. 23E